NUCLEOPHILIC ADDITIONS TO 3-AZIDO-HEXANAL

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NUCLEOPHILIC ADDITIONS TO 3-AZIDO-HEXANAL

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This research effort is dedicated to my parents,

Delores Schroeder and Everett Schroeder

ABSTRACT

Sakurai and Mukaiyama aldol additions were carried out with a *β*-azido aldehyde under chelation and non-chelation conditions. The reactions were generally found to be diastereofacially selective in favor of the *anti* stereoisomer and showed simple diastereoselectivity in favor *syn* substitution. The relative stereochemistry of the addition products were deduced from NOE experiments on cyclic amines that were produced from intramolecular Schmidt, Staudinger/aza-Wittig, and catalytic hydrogenation reactions. The findings indicate that substituted *N*-heterocycles can be made diastereoselectively in a couple of steps from simple azido aldehydes by carefully selecting the reaction conditions.

ACKNOWLEDGEMENTS

I would like to give thanks to my mother, Delores, for *always* believing in me and for giving me words of encouragement at times when I needed it the most. I also owe thanks to my heart and soul; my wife Laurie, my son Connor, and my daughter Haley for offering me patience, love, and support.

I am greatly thankful for the research opportunity Dr. Jeffrey Aubé has given me. Under his mentorship, I have been able to learn and conduct "world class" organic chemistry. Because of him, I now have the foundation necessary to do research in a field of science I truly love. Dr. Paul Hanson also deserves my gratitude for giving me an opportunity to work in his lab as an undergraduate when *no one* else would take a student lacking prior research experience. I am thankful to the Medicinal Chemistry department for providing me with a stipend.

I would also like to thank my past self for becoming interested in science and for setting a goal of obtaining a higher education 10 years ago. Lastly, for the additional encouragement, I would like to thank all of my friends in high school who thought I was dumb.

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INTRODUCTION

Methods for constructing complex organic molecules stereoselectively, and in a fast and efficient manner, are highly desirable and essential for the large scale synthesis of chiral natural products and pharmaceuticals. The process of introducing a new stereogenic center into a molecule is generally carried out using either reagent control, in which stereochemical information in the form of a chiral catalyst or additive is transferred to the substrate during the course of the reaction, or substrate control, in which new stereocenters are introduced stereospecifically to the substrate as a consequence of existing stereocenters in the starting material.[1,2] Alkyl azido aldehydes such as those used in this study represent a class of compounds that fall into the latter class. Nucleophilic additions to chiral azido aldehydes may be diastereoselective and yield products that are capable of cyclization into substituted *N*-heterocycles using a suitable ring-closing reaction. In particular, this thesis outlines the synthesis of 2,5-disubstituted 3-hydroxy pyrrolidines and 2,6-disubstituted 4-hydroxy piperidines.

A number of related heterocycles exhibit a diverse range of pharmacological activities (Figure 1). To name a few, (–)-codonopsinine is a pyrrolidine natural product that exhibits antibiotic and hypotensive activity in animal tests.[3] Alkaloid (+)-241D was isolated from the frog species, *Dendrobates speciosus* and has shown strong affinity to nicotinic receptors.[4] The 2,4-disubstituted piperidine, WO 2004/094380, is a pharmaceutical 5-HT_{1F} agonist that is used for the treatment of migraines.[5]

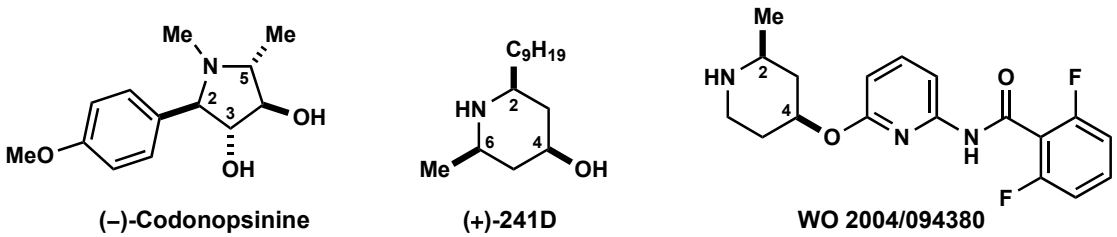
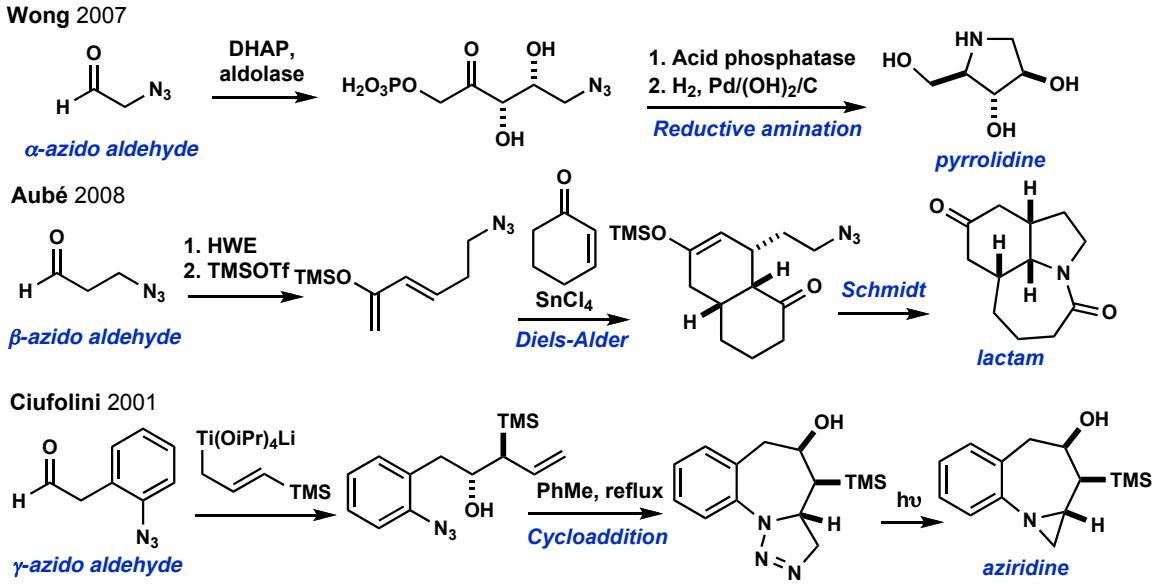


Figure 1. Relevant bioactive *N*-heterocycles.

Nucleophilic addition is one of many reactions capable of functionalizing an azido aldehyde for *N*-heterocyclic synthesis. Only a few reaction steps are necessary to convert an azido aldehyde into substrates suitable for practical ring-closing reactions. Beautiful examples from the literature exemplify how simple alkyl azides are capable of intramolecularly reacting with neighboring functional groups.

For example, the Wong group has done extensive studies on aldolase-catalyzed additions to α-azido aldehydes that yield polyhydroxylated azido ketones. These were reductively aminated under enzyme and hydrogen catalytic conditions to yield substituted pyrrolidines (Scheme 1).[6] By carefully selecting the reaction conditions, the Aubé group was able to quickly convert β-azido propanal into an azido diene, and submit it to a tandem Diels-Alder/Schmidt reaction, thus producing a tricyclic lactam diastereoselectively.[7] Another common intramolecular reaction used with linear azides is the [3+2] cycloaddition, which yields cyclic triazene products under thermal conditions. By using this reaction on azido allylsilanes derived from γ-azido aldehydes, the Ciufolini group decided to fragment the triazene intermediates under photolytic conditions to generate aziridines with the liberation of nitrogen gas (Scheme 1).[8]

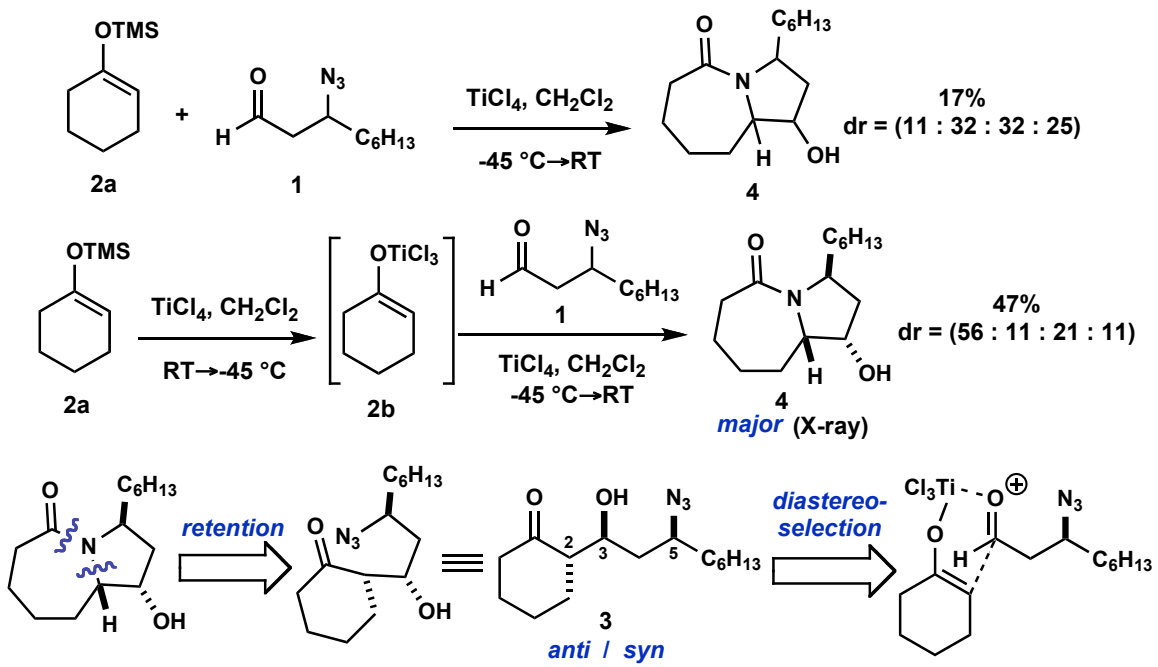
Scheme 1



Project background. Unpublished results from the Aubé group demonstrated the ability of azido aldehydes to participate in diastereoselective reactions.[9,10] A tandem Mukaiyama aldol/Schmidt reaction was achieved using *β*-azido nonanal **1** and silyl enol ether **2a** to produce all four diastereomers of bicyclic lactam **4** with low selectivity (Scheme 2). However, higher diastereoselectivity and yields of **4** were obtained by preparing the nucleophile as a titanium metal enolate **2b** (Scheme 2).

Aldol addition to **1** formed a *β*-hydroxy-*δ*-azido ketone intermediate **3** that subsequently reacted *in situ* to form product **4** upon stirring at room temperature. The relative stereochemistry of the major diastereomer was deduced from a X-ray crystal structure. The relative configuration displayed in the product was directly transferred from the aldol intermediate **3**, since the intramolecular Schmidt reaction is well known to give products with retention of stereochemistry.[11] Simple diastereoselection is observed in **3** by the *anti* substitution of C-2 and C-3 (Scheme 2). Facial diastereoselection is reflected in the *syn* substitution between C-3 and C-5.

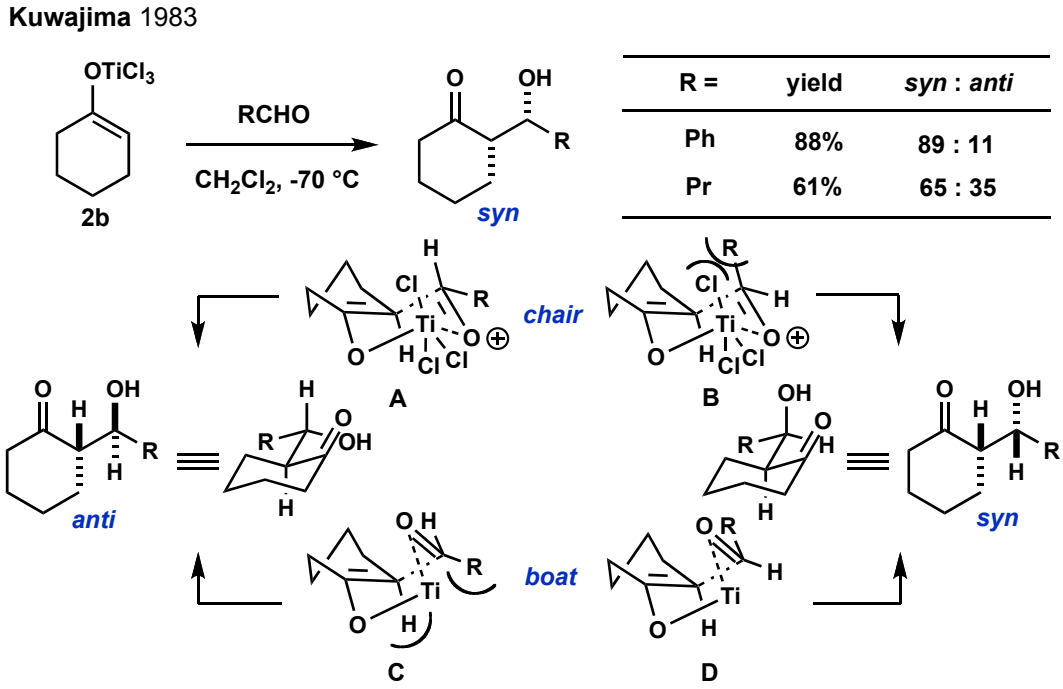
Scheme 2



Closed transition state models have been designed to rationalize the simple diastereoselection of prochiral aldol reactions. Metal enolate additions with aldehydes adopt either a chair or boat conformation. The Kuwajima group reacted the titanium enolate **2b** with simple aldehydes and observed the selective formation of the *syn* diastereomer in contrast to the expected *anti* diastereomer predicted for (*E*)-enolates (Scheme 3).[12] The chair conformation is usually used to rationalize the relative stereochemistry of aldol products arising from metal enolates. (*E*)-Enolates are predicted to go through the transition state **A** and yield *anti* selective products (Scheme 3). The chair conformation **B**, in which the alkyl group of the aldehyde assumes an axial position, would be relatively higher in energy and thus is a less likely transition state. Kuwajima and Nakamura have proposed the alternative boat transition state as an explanation for the selective formation of *syn* products arising from the aldol addition of **2b** to benzaldehyde and butanal (Scheme 3).[12,13] The authors propose the boat transition state

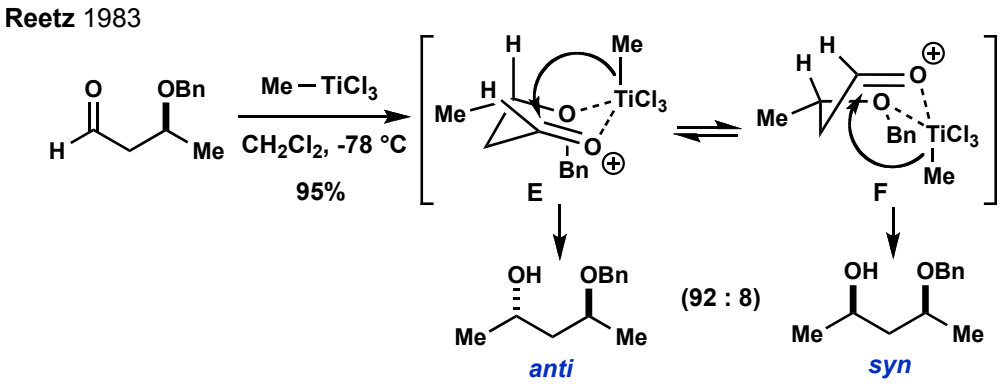
D, in which the nucleophile is reacting with the carbonyl at the Bürgi/Dunitz angle of attack and is relatively free of strain, as a plausible explanation for the observed stereochemical outcome. Steric interactions between the reactants in the boat conformation **C** would raise the energy of the transition state and is therefore less favorable than conformation **D**.

Scheme 3



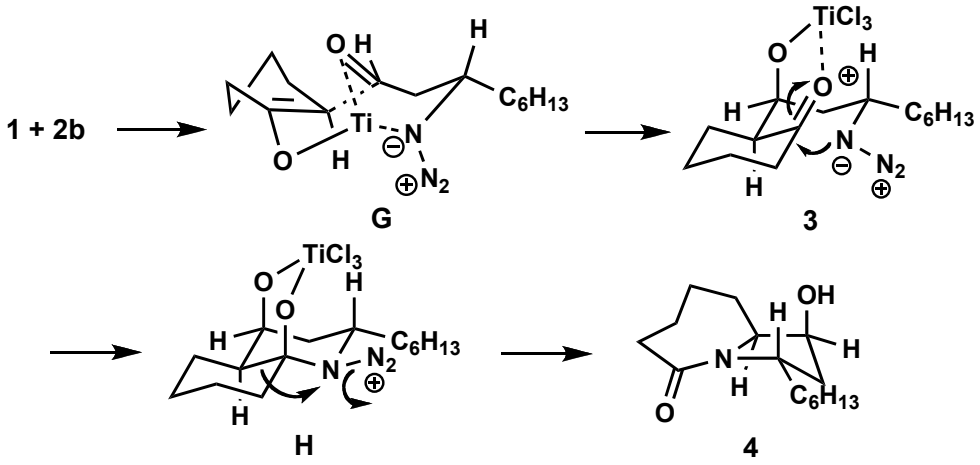
Facial diastereoselection in $TiCl_4$-mediated additions to β-heteroatom substituted aldehydes can also be rationalized along similar lines. The Reetz group reacted alkyl titanium reagents with β-alkoxy aldehydes and used the chair conformation **E** to explain the selective formation of 1,3-*anti* products (Scheme 4).[14]

Scheme 4



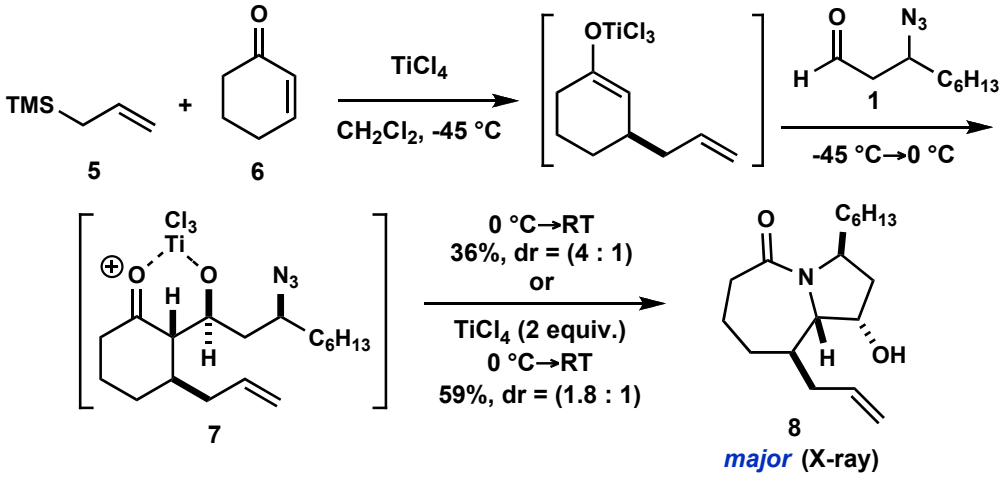
It is possible that the aldol reaction of *β*-azido nonanal **1** and titanium enolate **2b** progressed via a chelation adduct, in which the metal center is tri-coordinated with the enolate and the carbonyl and azido groups of the aldehyde. The transition state **G** explains the diastereoselectivity of the aldol reaction to produce the *anti*/*syn* intermediate **3** (Scheme 5). By coordinating to titanium, the enolate and azido aldehyde assume boat conformations similar to **C** (Scheme 3) and **F** (Scheme 4). Note the chelation in conformation **G** reverses the simple and facial diastereoselectivity by compromising the electrostatic interactions in conformations **C** and **F**. The intramolecular Schmidt reaction could then proceed through the transition state **H** en route to the lactam **4**. It is not known to what extent the titanium center is chelated in this reaction; the bidentate version shown is one of several possibilities.

Scheme 5



Similar diastereoselectivity was obtained using a tandem Sakurai/aldol/Schmidt reaction.[15] The Sakurai reaction was initiated by premixing allyl silane **5** with cyclohexenone **6** and $TiCl_4$ at -45 °C to generate a 1,4-conjugate intermediate (Scheme 6).[16] *β*-Azido nonanal **1** was added to the reaction mixture at 0 °C to produce the aldol intermediate **7**, which cyclized to the lactam product **8** upon warming to room temperature. The relative stereochemistry of the major diastereomer (36% yield, dr = 4:1) was determined by X-ray. Product yields were increased to 59% by adding more $TiCl_4$ to intermediate **7** before warming to room temperature, albeit with lower diastereoselectivity (dr = 1.8:1). Note, the relative stereochemistry of the major diastereomer **8** is analogous to that of lactam **4**. This suggests that intermediate **7** was generated by an aldol addition with a transition state like **G** (Scheme 5). The tandem reactions in both of these examples proceeded with *anti* simple diastereoselectivity and *syn* diastereofacial selectivity.

Scheme 6

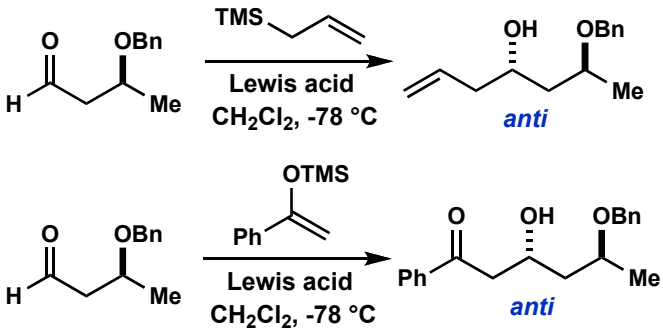


A great opportunity to further explore the selectivity and utility of nucleophilic additions to a *β*-azido aldehyde exists based on these findings and is the focus of this thesis. Sakurai and Mukaiyama aldol additions were carried out with *β*-azido hexanal **9** under chelation and non-chelation conditions. The *β*-azido alcohol products were cyclized to form *N*-heterocycles, which were used to determine the relative configuration of the addition products. The results obtained from this study will be used for comparison to the few examples provided in the literature of nucleophilic additions to *β*-azido aldehydes.

Facial diastereoselectivity in 1,3-asymmetric stereoinductions. The pioneering work of Reetz[14,17-21] and Evans[22-24] has provided a plethora of examples of 1,3-asymmetric nucleophilic additions to alkyl aldehydes bearing a substituted *β*-heteroatom stereocenter. Regardless of the chelation capability of the Lewis acid used, the products generally exhibit *anti* diastereofacial selectivity. For example, the Reetz group achieved high *anti* diastereoselectivity with Sakurai and Mukaiyama aldol additions to a *β*-alkoxy aldehyde using $TiCl_4$ and BF_3•OEt_2 Lewis acid reagents (Scheme 7).[14,19]

Scheme 7

Reetz 1984

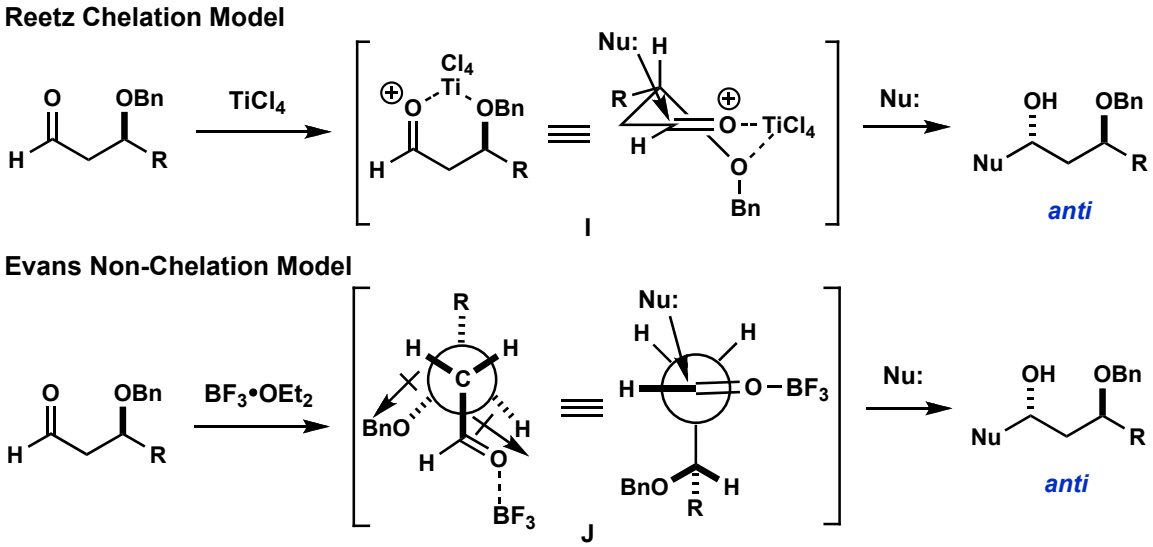


Lewis acid	yield	*anti* : *syn*
$TiCl_4$	85%	95 : 5
BF_3•OEt_2	NA	85 : 15

Lewis acid	yield	*anti* : *syn*
$TiCl_4$	95%	92 : 8
BF_3•OEt_2	82%	85 : 15

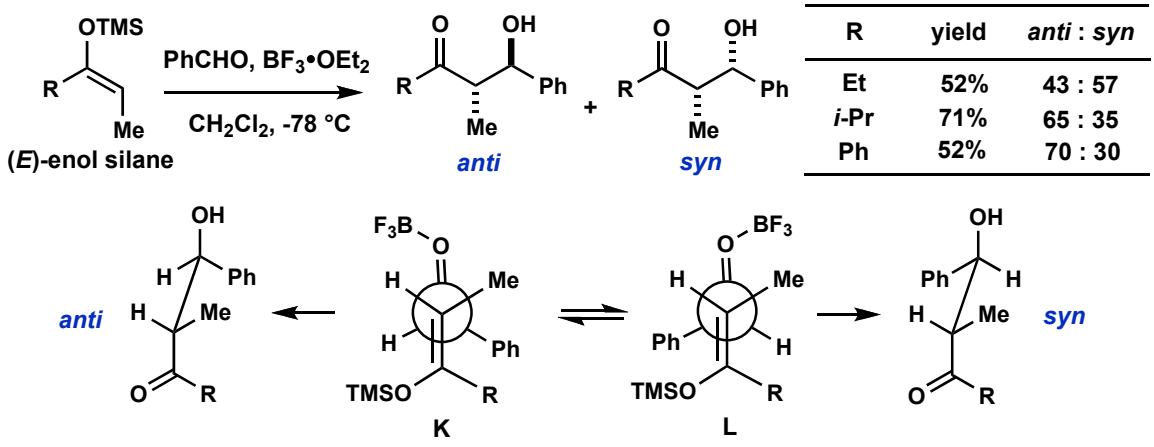
Two main models that are consistent with these results have been proposed (Scheme 8). Models for additions using chelation-capable Lewis acids such as $TiCl_4$, suggest that the carbonyl and heteroatom chelate with the metal center and force the aldehyde into a half-chair conformation **I**, thus biasing the π-face to selective nucleophilic attack.[14,17,19] Alternatively, the similar results obtained with Lewis acids incapable of chelation, such as BF_3•OEt_2, have been explained by a mechanism in which dipoles are minimized in the transition state **J**.[23]

Scheme 8



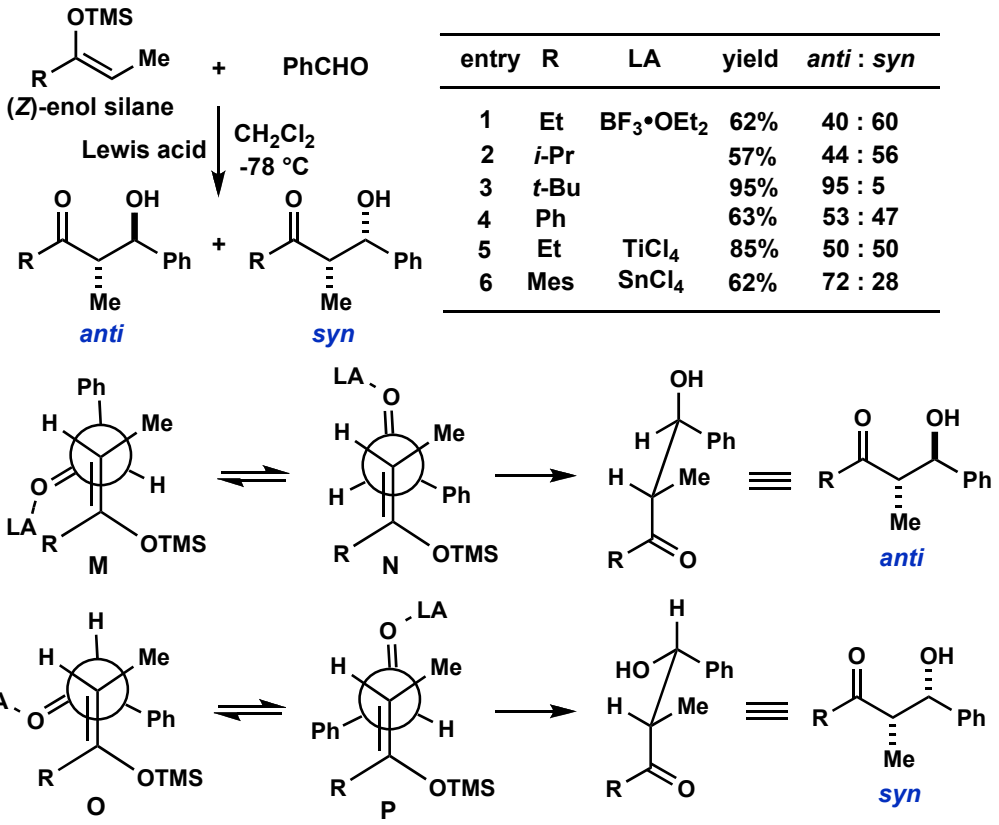
Simple diastereoselectivity in 1,2-asymmetric stereoinductions. Mukaiyama aldol additions can also be selective like their metal enolate counterparts. For example, the reaction of the cyclic enol silane **2a** with benzaldehyde and $TiCl_4$ at -78 °C afforded the keto alcohol product in a diastereomeric ratio of *anti*:*syn* = 75:25.[25] Note the reversal in selectivity when comparing the related addition of enolate **2b** to benzaldehyde (*anti*:*syn* = 11:89, Scheme 3). Simple diastereoselectivity of Mukaiyama aldol additions towards normal aldehydes is highly dependent on steric interactions between the enol silane, aldehyde, and Lewis acid.[26] Regardless of the enol silane geometry, higher selectivities were discovered when the R group of the enol silane was changed to more sterically bulky groups (Scheme 9). Heathcock and coworkers reacted various (*E*)- and (*Z*)-enol silanes with benzaldehyde and $TiCl_4$ at -78 °C and recorded the diastereomeric ratios.[27] For BF_3•OEt_2-mediated additions of (*E*)-enol silanes to benzaldehyde, selectivities reversed and increased in favor of the *anti* diastereomer as the size of the R group was increased from ethyl to isopropyl and phenyl (Scheme 9). Transition states **K** and **L** are close in energy for (*E*)-enol silanes and as a consequence selectivities are generally low.

Scheme 9



The same correlation between selectivity and the size of enol silane substituents was discovered for (*Z*)-enol silanes in the Mukaiyama aldol reaction (Scheme 10).[27] When R of the (*Z*)-enol silane was relatively small, the reaction with benzaldehyde was practically nonselective with a low preference for *syn* substitution (entries 1, 2 and 4). Yamamoto and Maruyama also found the reaction to be nonselective when $TiCl_4$ was used as the Lewis acid (entry 5).[28] However, high *anti* selectivity was produced in the aldol reaction once R was changed to the sterically bulky groups *tert*-butyl and mesityl (entries 3 and 6) regardless of the Lewis acid used. Based on this finding, Heathcock and coworkers rationalized the increased *anti* selectivity based on a series of open transition states (Scheme 10).[27] Not shown are the unfavorable transition states in which dipole-dipole interactions exist. For the *tert*-butyl substituted (*Z*)-enol silane (entry 3), transition states **M** and **P** are disfavored due to steric interactions caused by *tert*-butyl between the Lewis acid and phenyl group, respectively. Transition state **N** is favored over **O**, which has two nonbonded interactions between *tert*-butyl and the carbonyl and between the siloxy and phenyl groups.

Scheme 10

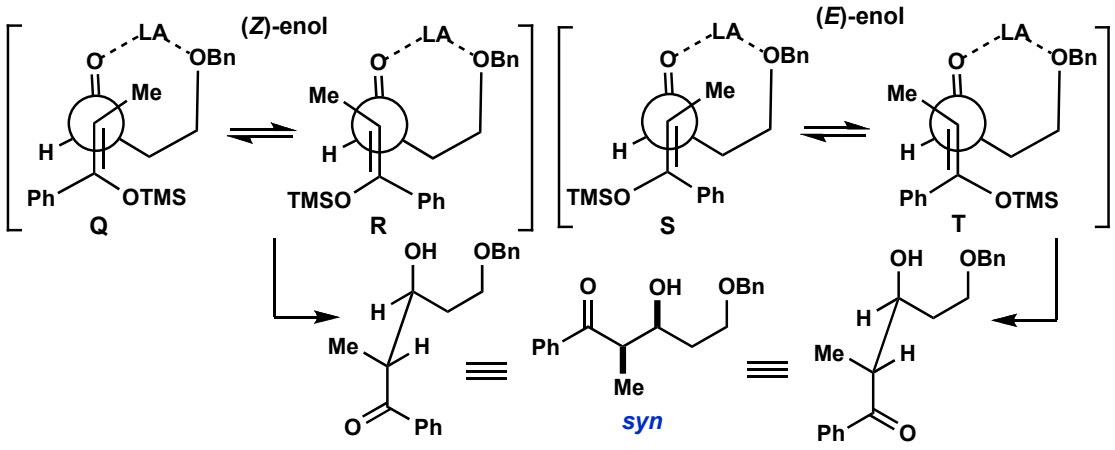


entry	R	LA	yield	*anti* : *syn*
1	Et	BF_3•OEt_2	62%	40 : 60
2	*i*-Pr		57%	44 : 56
3	*t*-Bu		95%	95 : 5
4	Ph		63%	53 : 47
5	Et	$TiCl_4$	85%	50 : 50
6	Mes	$SnCl_4$	62%	72 : 28

Diastereoselectivity is generally much higher when the aldehyde is capable of chelation to the Lewis acid. Hence, simple diastereoselectivity is quite predictable for Mukaiyama aldol additions of prochiral silyl enol ethers to *β*-heteroatom-substituted aldehydes. The stereochemical configuration observed in the products is also consistently *syn* regardless of the geometry of the silyl enol ethers used or the chelating ability of the Lewis acid.[17] An open transition state model, in which the Lewis acid chelates with the carbonyl and *β*-heteroatom of the aldehyde, is used to explain the preference for *syn* products (Scheme 11). Steric interactions between the methyl and Lewis acid in transition states **Q** and **S** for both (*Z*)- and (*E*)-enol silanes is energetically unfavorable. Transition states **R** and **T** readily explain the convergent *syn* simple

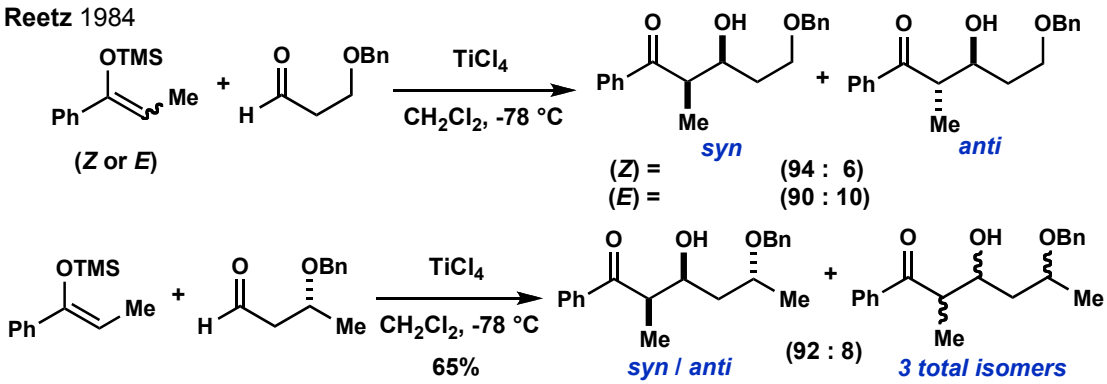
diastereoselectivity observed in Mukaiyama aldol additions to β-heteroatom-substituted aldehydes.[26]

Scheme 11



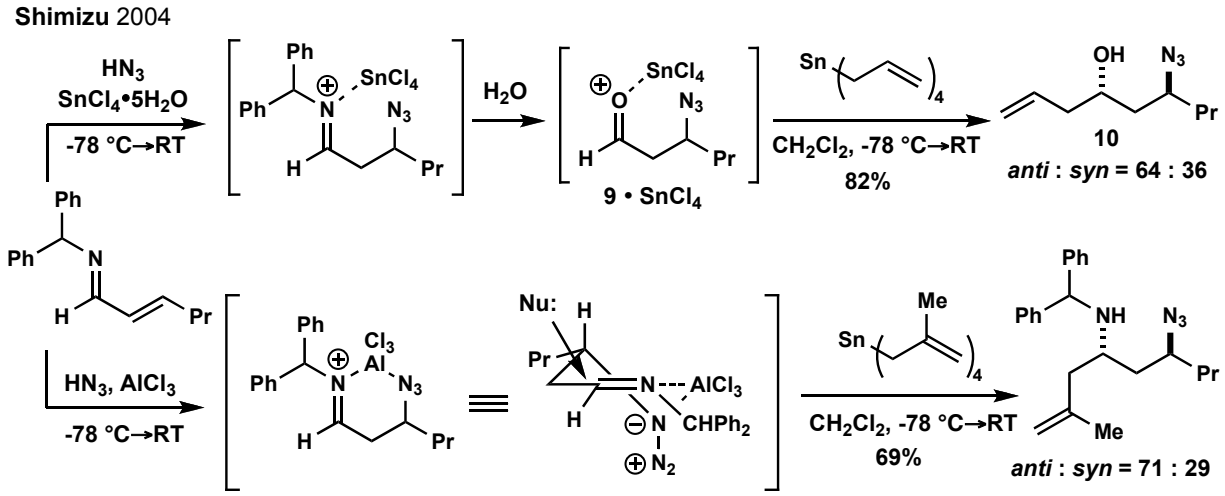
Reetz showed that high *syn* simple diastereoselectivity could be achieved with Mukaiyama aldol additions to a β-alkoxy aldehyde regardless of the enol silane double-bond geometry (Scheme 12).[17] Both silyl enol ethers afforded the *syn* diastereomer in at least a 9:1 ratio. Nucleophilic additions to β-heteroatom-substituted aldehydes are thus predicted to yield products with both *anti* diastereofacial selectivity and *syn* simple diastereoselectivity when prochiral enol silanes are used. An example from the Reetz group illustrates this point. Mukaiyama aldol addition of a (*Z*)-enol silane to the substituted β-alkoxy aldehyde under chelation conditions produced predominantly one out of four possible stereoisomers (Scheme 12).[20] This reaction was highly diastereoselective (92%) for the predicted *syn*/*anti* stereoisomer.

Scheme 12



Nucleophilic additions to *β*-azido aldehydes. Only a few examples of nucleophilic additions to *β*-azido aldehydes exist in the literature. Allyl additions to *β*-azido hexanal **9** has been accomplished by the Shimizu and Kim laboratories. The Shimizu group generated **9** *in situ* from the equivalent aldimine (Scheme 13).[29] This was carried out by conjugate addition of hydrazoic acid to **9** and subsequent hydrolysis with $SnCl_4 \bullet 5H_2O$. Under these chelating conditions, addition of an allyl group via tetraallyltin gave a series of 1,3-azido alcohols with moderate *anti* diastereofacial selectivity. By changing the Lewis acid to $AlCl_3$ they were able to intercept the saturated 1,3-azido imine with tetraallyltin, thus providing 1,3-azido amines that were also *anti* diastereofacial selective.[30] A half-chair transition state, in which the metal center is chelating with the iminyl and azido groups, was used to explain the *anti* diastereoselectivity (Scheme 13). The Kim group allylated **9** with allyl bromide and indium to give the 1,3-azido alcohol **10** with fairly low stereoselectivity (*anti*:*syn* = 60:40).[31]

Scheme 13

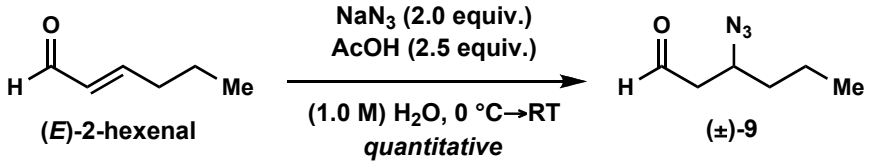


This thesis describes the results of nucleophilic additions of allyl and enol silanes to β-azido hexanal **9** under chelation ($TiCl_4$) and non-chelation (BF_3•OEt_2) conditions. The products thus obtained were cyclized to form rigid *N*-heterocycles suitable for proof of relative stereochemistry via 1D NOE experiments. The results obtained from this study will be used for comparison to the few examples provided in the literature of nucleophilic additions to β-azido aldehydes.

RESULTS AND DISCUSSION

β-Azido hexanal **9** was the electrophile used in this study for nucleophilic additions and was generated from (*E*)-2-hexenal using slightly modified Boyer conditions (Scheme 14).[32] Hydrazoic acid was generated *in situ* from acetic acid and sodium azide under aqueous conditions. It is worth noting that azido aldehyde **9** is unstable, and quickly decomposes to a dark red oil, especially at room temperature.[10] Therefore, only freshly prepared **9** was used in this study.

Scheme 14



Sakurai reaction. Initially, nucleophilic additions to **9** were carried out under Sakurai allylation conditions. The reactants were mixed in CH_2Cl_2 at -78 °C prior to Lewis acid addition. The results are shown in Table 1. Diastereomeric ratios were determined from crude reaction mixtures by ^{1}H NMR (Figure 2) and the relative stereochemistry of **10a** and **10b** was assigned as previously reported in the literature.[29]

When BF_3•OEt_2 was used as the Lewis acid, good diastereofacial selectivity was observed in the direction of the predicted stereoisomer with a ratio of *syn*:*anti* = 18:82. However, when using a chelating Lewis acid ($TiCl_4$), diastereofacial selectivity was reversed. A moderate yield was observed and the *syn* diastereomer predominated with a ratio of *syn*:*anti* = 62:38.

Table 1. Sakurai allylation to *β*-azido hexanal **9**.

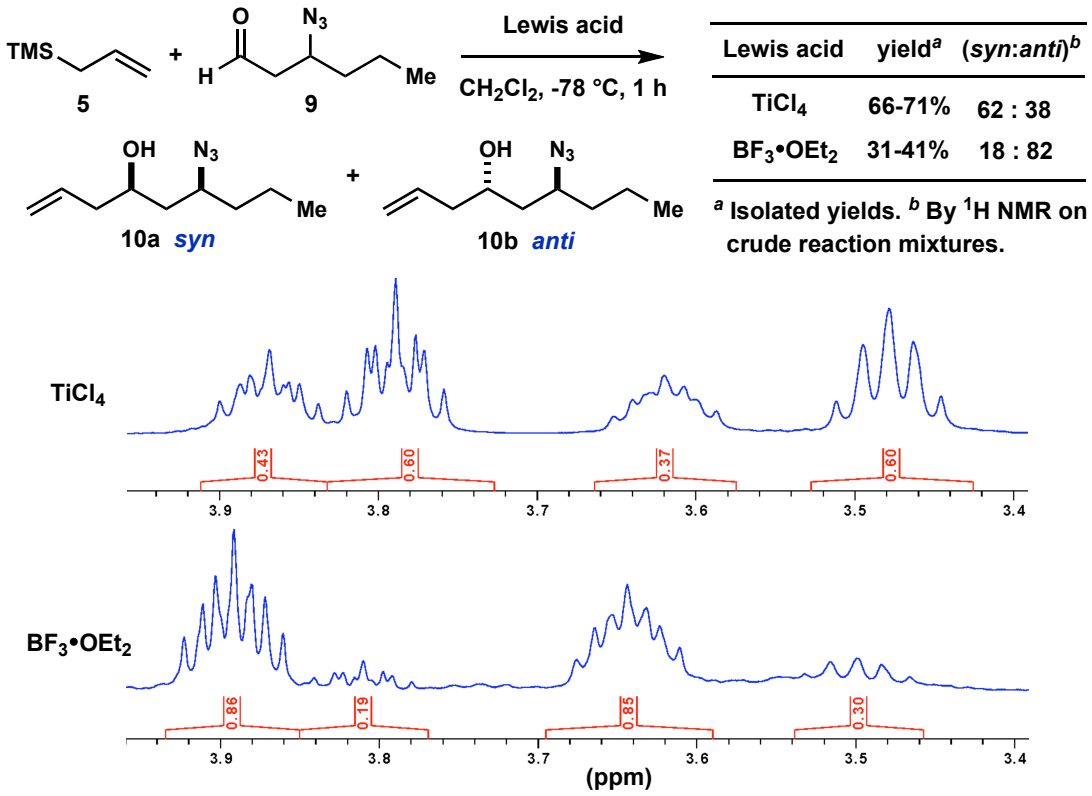


Figure 2. ^{1}H NMR spectra of the crude reaction mixture **10**. The diastereotopic H-C-OH proton peaks (one from each diastereomer) are downfield relative to the H-C-N_3 proton peaks (one each), which are upfield.

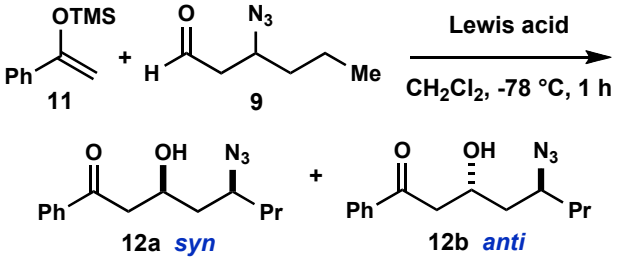
The stereochemical outcome is similar to that observed in the aldol/Schmidt domino reactions and suggests that the half-chair coordination **I** (Scheme 8) with $TiCl_4$ is indeed not operating in this case and that the azido group is not chelating with the Lewis acid during nucleophilic attack on the carbonyl. It is quite possible that a more complex mechanism is dominating the reaction course in this particular case.[33]

Mukaiyama aldol reaction. Enol silane **11**, derived from acetophenone, was the next nucleophile to be explored in additions to **9**. Mukaiyama aldol addition did not proceed under standard reaction conditions, in which the aldehyde was mixed with the

Lewis acid at -78 °C prior to addition of the enol silane.[25] A similar finding was reported by Heathcock and coworkers, who noticed that premixing benzaldehyde and $TiCl_4$ before enol silane addition caused a precipitate to persist in the reaction and gave irreproducible results.[27] Similarly, no reaction was observed when the enol silane was premixed with the Lewis acid, followed by aldehyde addition. In contrast, mixing the enol silane **11** with the aldehyde **9** in CH_2Cl_2 at -78 °C prior to slow addition of $TiCl_4$ afforded products as shown in Table 2. After 1 h, the reaction was carefully quenched with aqueous NH_4Cl as the flask was being removed from the Dewar cold bath (c.a. -78 °C).

Both of the Lewis acids employed in the aldol addition gave complimentary results with regard to the diastereofacial selectivity, which was in favor of the *anti* diastereomer **12b** (Table 2). In fact, the diastereomeric ratios, as well as the isolated yields, were almost identical. Using $TiCl_4$ as the Lewis acid gave a ratio of *syn*:*anti* = 23:77, and BF_3•OEt_2 gave a ratio of *syn*:*anti* = 22:78, both in moderate yields. Insufficient separation of diastereomeric proton peaks were observed in the ^1H NMR spectrum of **12**, thus isomer ratios were obtained using analytical HPLC chromatograms of the crude reaction mixtures (Figure 3). In contrast to the results obtained from the Sakurai reaction, the Mukaiyama aldol addition showed the *anti* diastereofacial selectivity expected from the Reetz/Evans transition state models used for nucleophilic additions to β-heteroatom-substituted aldehydes using both chelating and non-chelating Lewis acids.

Table 2. Mukaiyama aldol addition of **11** to **9**.



Lewis acid	yield[a]	dr (*syn* : *anti*)[b]
$TiCl_4$	46-52%	23 : 77
BF_3•OEt_2	55-66%	22 : 78

[a] Isolated yields. [b] By HPLC on crude reaction mixtures.

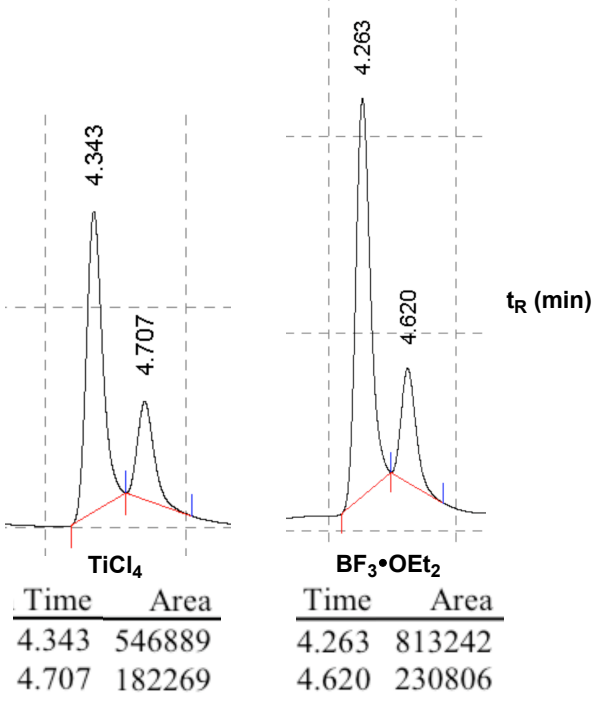
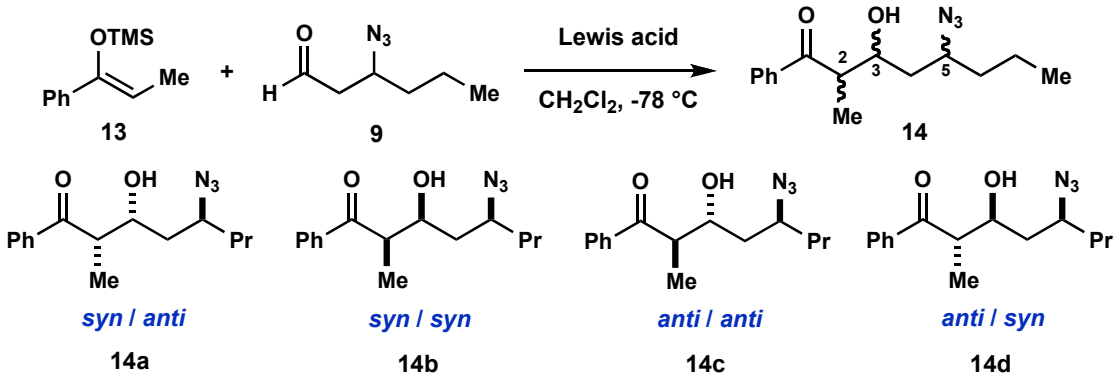


Figure 3. HPLC chromatograms of the crude reaction mixture **12**.

The (*Z*)-enol silane **13**, derived from propiophenone, was the next nucleophile chosen for aldol addition. Mukaiyama aldol addition of **13** to azido aldehyde **9** was carried out under the same two sets of conditions that were used with enol silane **11**. All four of the possible stereoisomers **14a-d** were produced with the ratios given in Table 3. However, when stoichiometric amounts of $TiCl_4$ and **13** were used, incomplete conversion to the azido alcohol product **14** was observed in the crude ^{1}H NMR spectrum (entry 1). A few changes in reaction conditions were then tried in order to increase the conversion levels. Increasing the reaction time slightly elevated the conversion level

(entry 2), while larger equivalents of $TiCl_4$ showed no effect (entry 3). Full conversion was not realized until the equivalents of $TiCl_4$ and **13** were both doubled (entry 4). Mukaiyama aldol addition using stoichiometric amounts of BF_3•OEt_2 and **13** produced **14** with full conversion and moderate isolated yield (entry 5).

Table 3. Mukaiyama aldol addition of **13** to **9**.

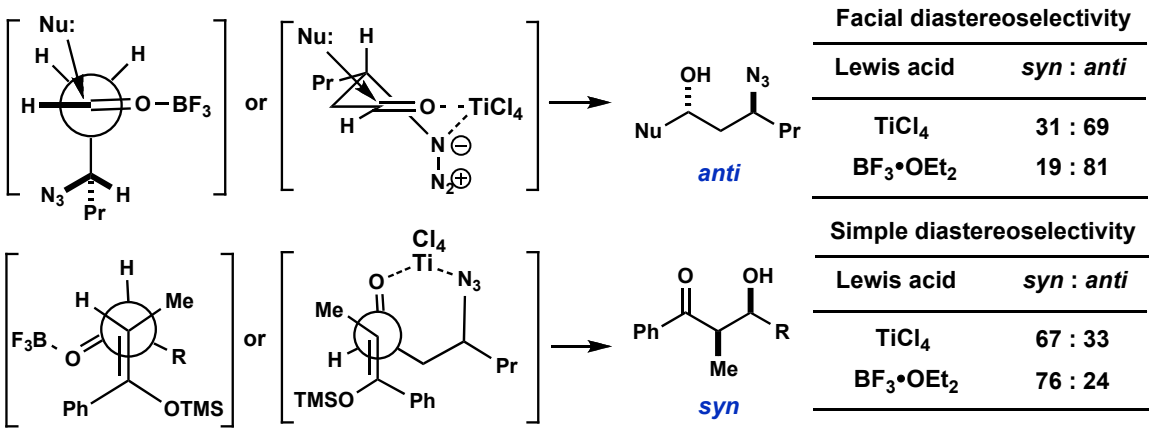


entry	Lewis acid (equiv.)	enol (equiv.)	time	conv.[a]	14 dr[a] (a : b : c : d)	yield[b]
1	$TiCl_4$ (1.1)	1.1	1 h	64%	(46 : 27 : 16 : 11)	31%
2	1.1	1.1	10 h	77%		
3	4	1.1	2 h	64%		
4	2	2	2 h	>95%	(50 : 17 : 19 : 14)	57%
5	BF_3•OEt_2 (1.1)	1.1	1 h	>95%	(62 : 14 : 19 : 5)	64%

[a] Determined by ^{1}H NMR on crude reaction mixtures. [b] Isolated yields.

The diastereomeric ratios given in Table 3 were determined by ^{1}H NMR on the crude reaction mixtures and indicate **14a** was the major diastereomer produced in this reaction regardless of the Lewis acid used. Diastereomers **14a**, **14b**, and **14c** were each isolated and cyclized to determine their relative stereochemistry by NOE (see below). The only diastereomer (out of four possible) left was assigned the relative stereochemistry shown for **14d**.

Overall, the direction of diastereoselectivity was indiscriminate of the Lewis acid used, although relatively higher with the BF_3•OEt_2-mediated addition. The total facial diastereoselectivity (relative C-3 hydroxy and C-5 azido groups) of the Mukaiyama aldol reaction was in favor of *anti* substitution (Figure 4). This finding is similar to the previously reported aldol addition of **13** to a *β*-alkoxy aldehyde.[20] Likewise, the total simple diastereoselectivity (between the C-2 methyl and C-3 hydroxy groups) from this reaction indicates that the aldol addition was *syn* selective.



Facial diastereoselectivity	
Lewis acid	***syn* : *anti***
$TiCl_4$	31 : 69
BF_3•OEt_2	19 : 81

Simple diastereoselectivity	
Lewis acid	***syn* : *anti***
$TiCl_4$	67 : 33
BF_3•OEt_2	76 : 24

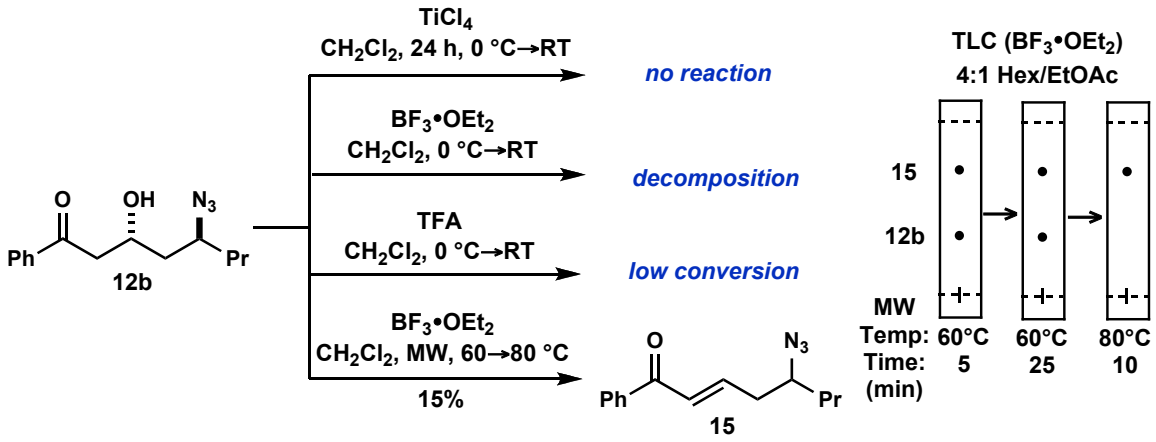
Figure 4. Total facial and simple diastereoselectivity of aldol addition **13** to **9**.

Schmidt cyclization. The Mukaiyama aldol products were cyclized in order to determine their relative stereochemistry. The *N*-heterocycles produced by ring closure are more conformationally rigid and thus more suitable for stereochemical determination using NOE. Three different ring-closing reactions were employed in this study to achieve this goal and to explore the synthetic utility of the addition products. The intramolecular Schmidt reaction,[34] the intramolecular Staudinger/aza-Wittig reaction,[35] and catalytic hydrogenation were chosen for study.

All attempts to cyclize major diastereomer **12b** under commonly used conditions for the intramolecular Schmidt reaction were unfruitful (Scheme 15). There was either

no reaction, decomposition of starting material, or low conversion to an undesired product **15**, when $TiCl_4$, BF_3•OEt_2, and TFA were used as activators, respectively. Isolated keto azide **12b** was heated in a microwave with BF_3•OEt_2 and monitored by TLC, which indicated that only one compound was being produced (Scheme 15). Upon purification, the compound was determined to be the dehydrated product **15**, presumably arising from the elimination of a hydroxide complex as promoted under the Lewis acid conditions. The diastereomer **12b** was cycled using the Staudinger/aza-Wittig reaction and will be discussed in a later section.

Scheme 15

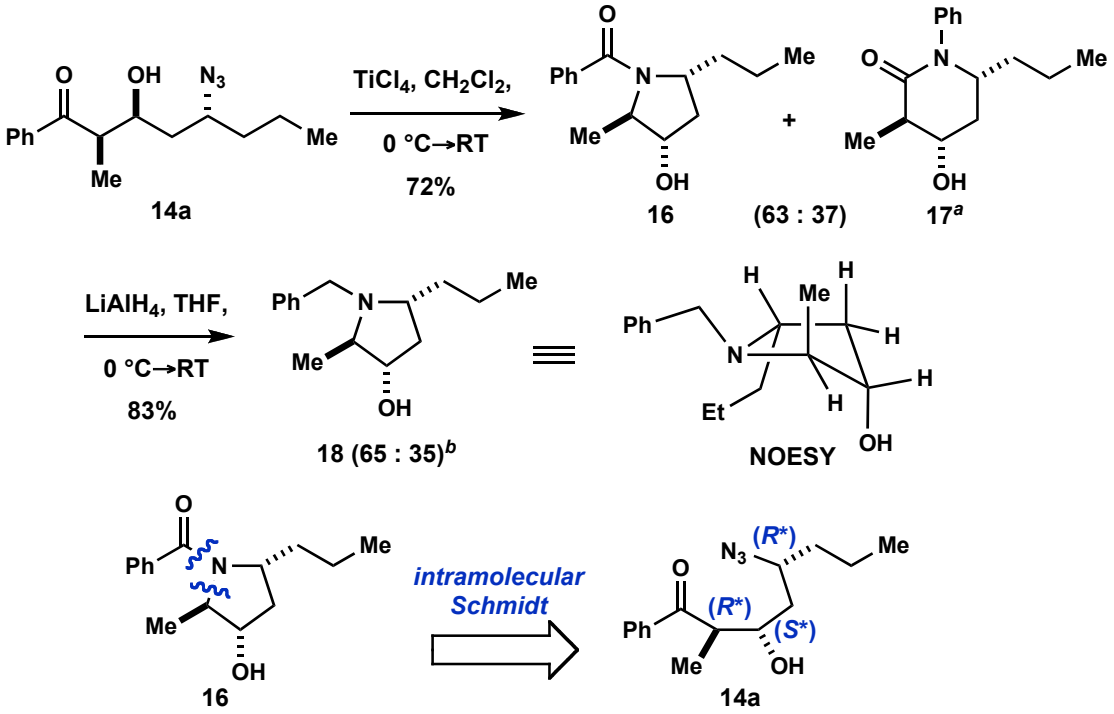


Identifying the relative stereochemistry of each aldol product **14a-d** diastereomer necessitates that a minimum of three out of four be elucidated (making experimental determination of stereochemistry in **14d** unnecessary). Logically, the initial focus towards this goal was on determining the relative stereochemistry of the major stereoisomer **14a**. Finding suitable conditions for efficient separation of diastereomers was only achieved after considerable time and effort and eventually a reliable protocol was used to isolate sufficient amounts of each diastereomer **14a**, **14b**, and **14c**.

Although the previous isomer **12b** did not undergo an intramolecular Schmidt reaction, isomer **14a** could be cyclized to *N*-benzoyl pyrrolidine **16**, upon treatment with $TiCl_4$ in CH_2Cl_2 (Scheme 16). The crude ^{13}C NMR spectrum of the Schmidt reaction indicated the presence of what appeared as two similar products with slightly offset chemical shifts. Instead of two products, the NMR peaks could be attributed to **16** as an equilibrium between two "rotamers" (*cis*/*trans* isomers), which is commonly observed in the NMR spectra of *N*-acyl pyrrolidines and piperidines.[36]

The question of whether one (rotamers) or two compounds had been produced was answered by reducing the amide to the corresponding amine. Thus, the Schmidt product **16** (^1H NMR ratio of 63:37) was chilled to 0 °C and stirred with $LiAlH_4$ in THF.[37] The ^1H NMR spectrum of the crude reaction sample showed the presence of two distinct products in a ratio of 65:35 (Scheme 16), indicating the ratio seen from the Schmidt reaction was indeed from two different compounds. The major product of the reduction was isolated and identified as pyrrolidine **18**, which was confirmed from NOESY interactions.

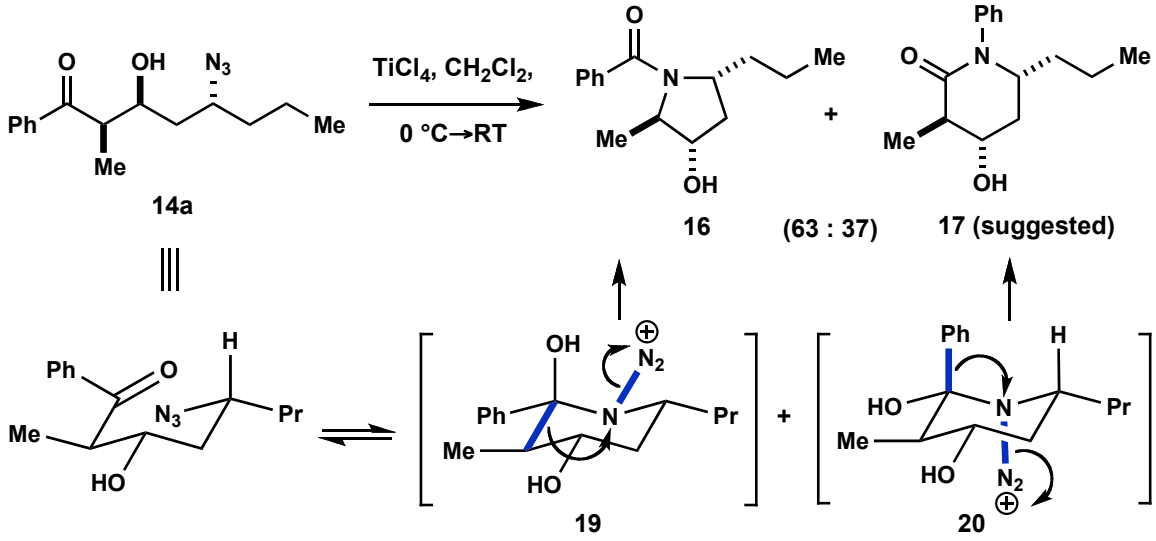
Scheme 16



[a] **Structure has not been experimentally proven, see Experimental section.**
[b] **Ratio was obtained from the crude reaction mixture.**

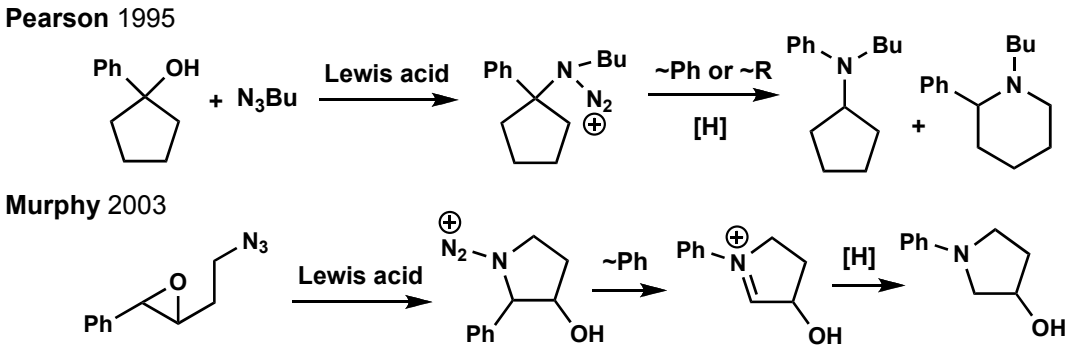
Isolation of the minor product proved to be much more difficult. Numerous attempts at separating it from **18** by flash column chromatography and preparative TLC were unsuccessful. However, one possible structure minor lactam **17** can be inferred by assuming that it was produced by taking another feasible pathway allowed by the intramolecular Schmidt reaction (Scheme 17).[11] Rearrangement in this pathway necessitates an antiperiplanar relationship between migrating bonds, which intermediates **19** and **20** both fulfill. Standard alkyl migration would account for the formation of **16**, whereas **17** forms only as the benefactor of a 1,2-phenyl shift.

Scheme 17



Instead of phenyl shifts, what is more commonly seen with linear, acyclic substrates are alkyl shifts, as well as hydride shifts in activated *δ*-azido aldehydes.[11,38] However, there are reported examples of phenyl shifts occurring with the other variants of the Schmidt reaction. The Pearson group found that both alkyl and phenyl migrations were occurring when alkyl azides were reacted with benzylic hydrins intermolecularly (Scheme 18).[39] The Murphy group primarily observed phenyl shifts taking place in the intramolecular Schmidt reactions of activated azido arylepoxides (Scheme 18).[40]

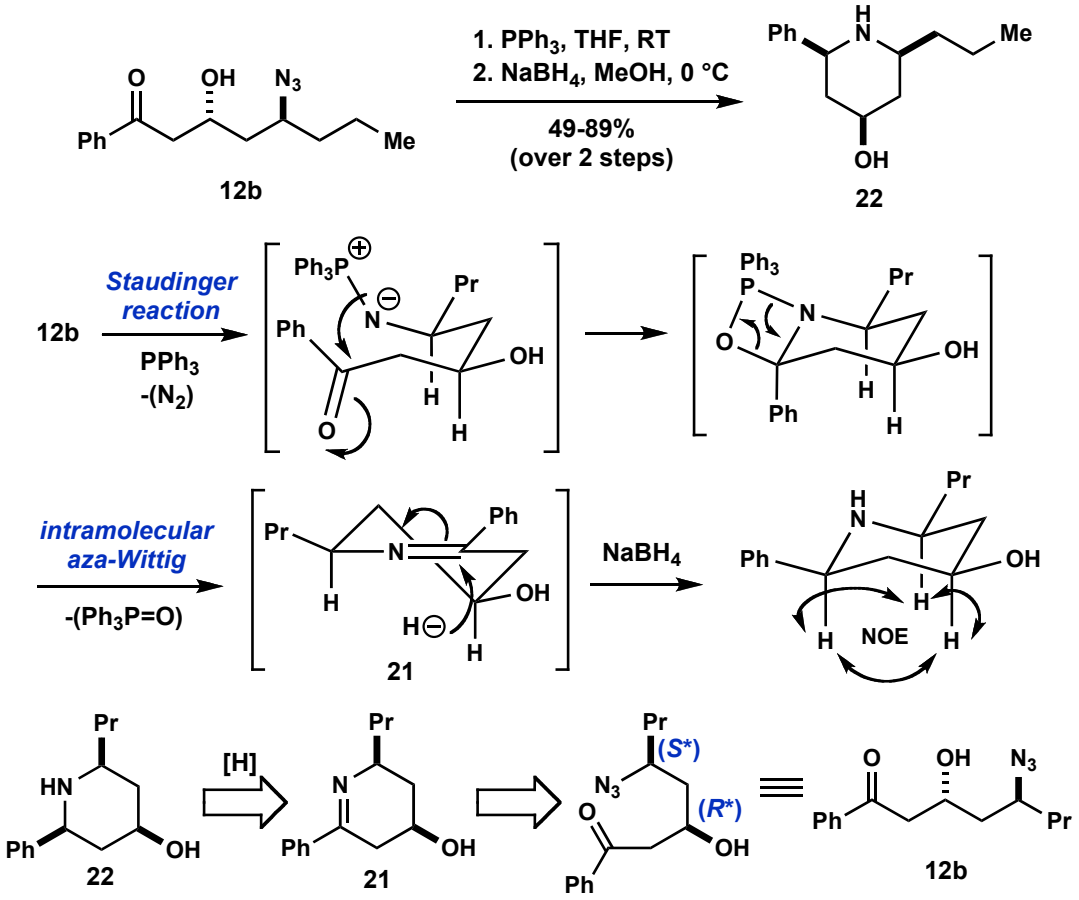
Scheme 18



The intramolecular Schmidt reaction was tried with the isolated minor diastereomer **14b**, which resulted in decomposition of starting material. No reaction was observed after **14c** was stirred with $TiCl_4$ at room temperature. In fact, this reaction was used to isolate **14c** from **14d** during one of the separation steps (see Experimental Section).

Staudinger/aza-Wittig cyclization. The relative stereochemistry of the major diastereomer **12b** (isolated from minor **12a** using CH_2Cl_2 on silica gel) could be determined by carrying out a Staudinger/aza-Wittig sequence to afford a piperidine derivative. This was accomplished by simply stirring **12b** and PPh_3 in THF. Although the ensuing cyclic imine **21** could be detected in the crude ^{13}C NMR spectrum ($\delta_{C=N}$ 163.2), it could not be isolated by flash chromatography. It presumably decomposed on silica gel via hydrolysis (^{13}C NMR, $\delta_{C=O}$ 200.4). Attention was then turned towards reducing the imine *in situ* and isolation of the corresponding piperidine **22** (Scheme 19). Stirring **12b** and PPh_3 in THF afforded **21**, which was reduced with $NaBH_4$ in one pot. Piperidine **22** could be purified by silica gel chromatography using 1:19:700 $NH_4OH/MeOH/CH_2Cl_2$ as the mobile phase.

Scheme 19



The relative *anti* stereochemistry of **12b** was determined by NOE studies on compound **22** (Figure 5). NOE experiments with **22** showed through-space interactions between the three triaxial protons indicating that the hydride attacked the imine π-face *trans* to the alkyl and hydroxy substituents. Irradiation of each axial proton (H^A, H^B, and H^C) caused enhancement of each of the other two axial protons. Irradiation of H^A also caused significant enhancement of all four methylene protons located on the nitrogen ring. Only H^B (out of three axial protons) caused enhancement of aromatic protons. NOE enhancement of methylene protons on the propyl group was also observed when H^C was irradiated.

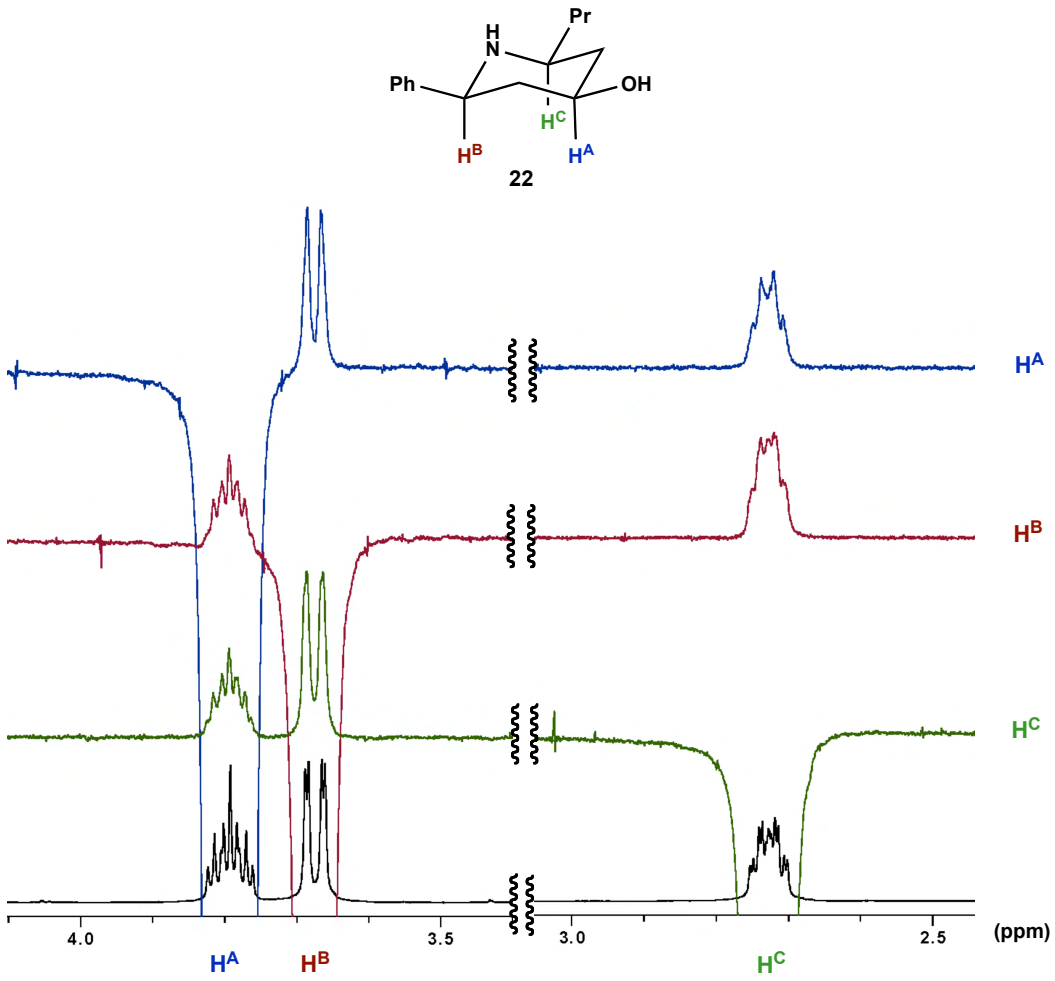


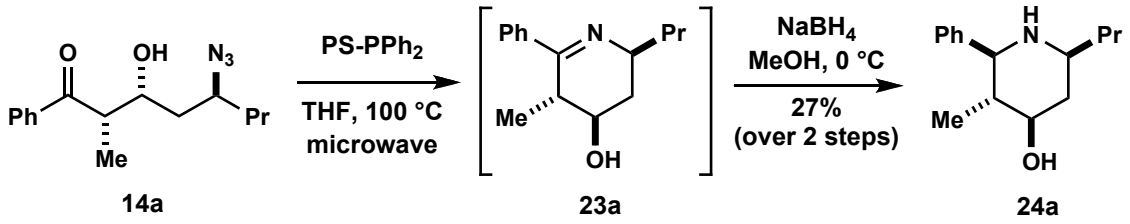
Figure 5. NOE experiments on piperidine **22**. Each proton (H^A, H^B, and H^C) was irradiated and caused enhancement of each of the other two axial protons.

The intramolecular Staudinger/aza-Wittig reactions with **14** were initially attempted on the mixture of **14a-d** following the standard procedure with PPh_3. However, the crude NMR spectrum was quite complex, which made the matching process of substrate to product diastereomers using ratios impractical. For that reason Staudinger/aza-Wittig reactions were carried out on diastereomerically pure samples of **14a-c**. In addition, it became apparent that one of the product diastereomers was coeluting with the triphenylphosphine oxide byproduct (see below). Therefore, resin-bound PPh_3 (PS-PPh_2) was used for the cyclization of the major diastereomer **14a**, which

allows the phosphine oxide byproduct to be easily separated from products using simple filtration.

Comparatively, the resin-bound reagent is less reactive, typified by low conversions to product when stirring at room temperature for an extended period of time. Thus, the substrate **14a** was stirred with PS-PPh_2 in THF and heated to 100 °C in a microwave reactor for 6 h (Scheme 20). At room temperature, the intermediate imine **23a** was filtered into another flask and then reduced with $NaBH_4$ at 0 °C. The product was isolated by flash chromatography and was consistent with the ^1H and ^{13}C NMR spectra for **24a**. The relative stereochemistry of **24a** was determined after being produced from **14a** using hydrogenolysis (see below).

Scheme 20

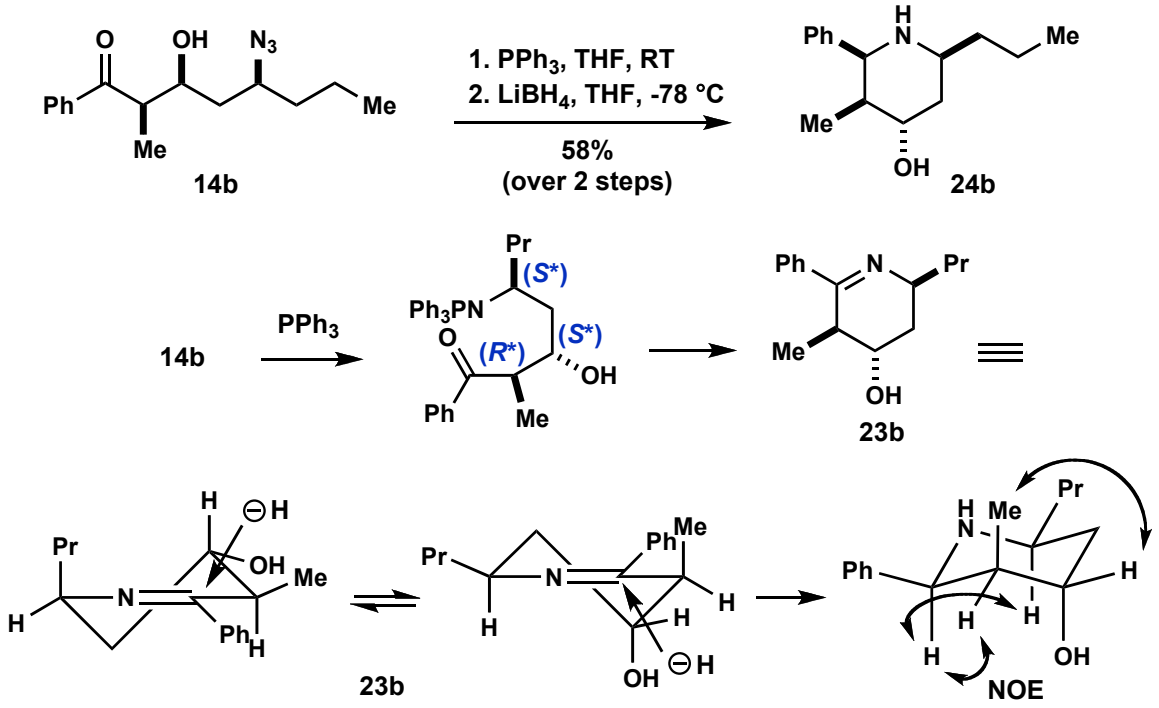


14a **23a** **24a**

The Schiff base **23b** was generated from **14b** under standard Staudinger conditions, stirring with PPh_3 in THF at room temperature. Reduction with $NaBH_4$ at 0 °C gave a compound as a mixture of at least two diastereomers (^1H NMR spectrum). It was therefore speculated that the diastereofacial selectivity of hydride attack on the imine double bond was low. The reduction was nonselective because the intermediate **23b** exists as an equilibrium of half-chair conformations (Scheme 21, boat conformations are also possible). The half-chair conformations are relatively close in energy since both have an alkyl group adopting an unfavorable axial position. Another approach involving a method for reducing cyclic imines was then attempted.

The substrate **23b** was again prepared by stirring **14b** and PPh_3 in THF at room temperature and then reduced with $LiBH_4$ at -78 °C.[41] Following a reaction quench, ^1H NMR analysis of the crude reaction mixture was conducted and indicated that the only substances present in the mixture was one new compound, the phosphine byproduct, and some THF. The product was readily isolated by flash chromatography and assigned the relative configuration shown for **24b** based on the NOE spectra of relevant, irradiated protons (Scheme 21). This information was used to assign the relative stereochemistry of **14b**, having all three substituents in a *syn* relationship.

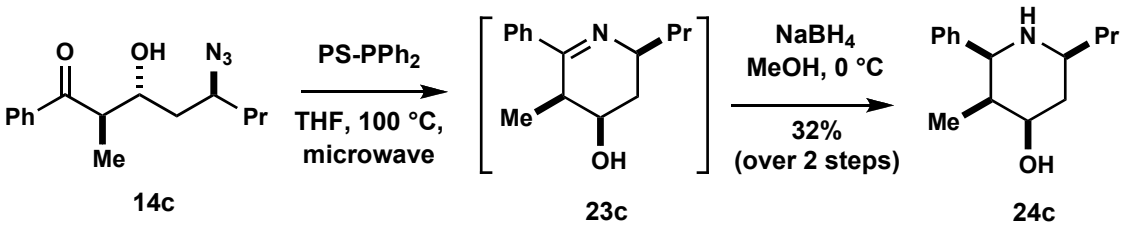
Scheme 21



Recall that one of the diastereomeric products of the Staudinger/aza-Wittig reaction on the mixture of **14** was coeluting with triphenylphosphine oxide in chromatographic fractionations. That compound was determined to be the product **24c**. Minor diastereomer **14c** was stirred with PS-PPH_2 in THF and microwaved to 100 °C.

The mixture was filtered and then reduced with $NaBH_4$ at 0 °C (Scheme 22). The desired product **24c** was subsequently isolated by flash chromatography. The relative stereochemistry of **24c** was determined after being produced from **14c** using hydrogenolysis (see next section).

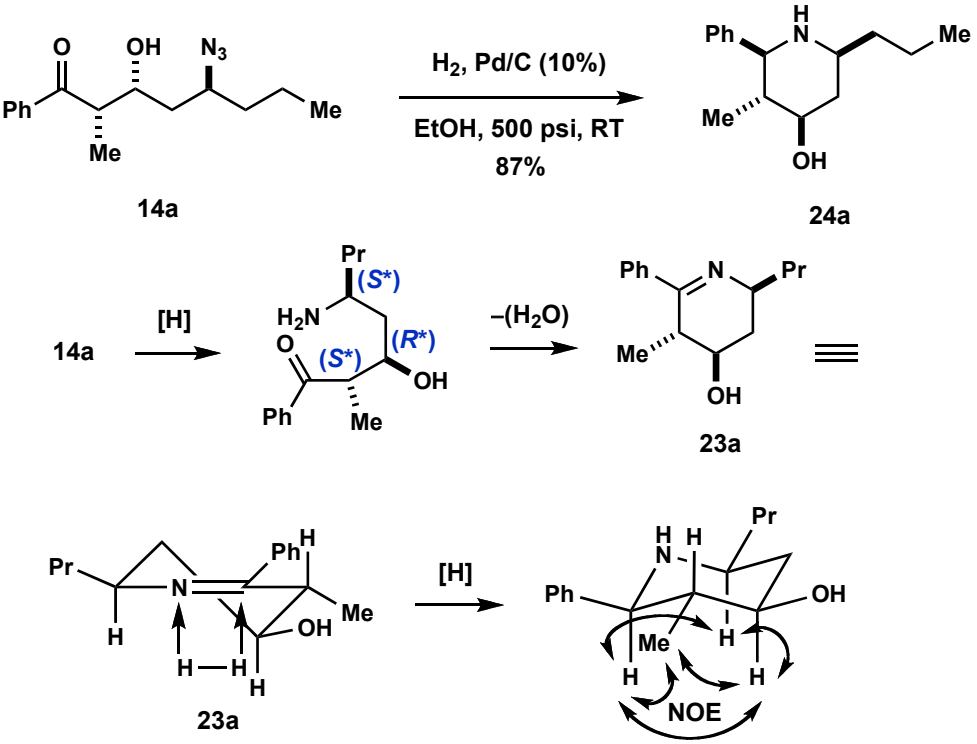
Scheme 22



Catalytic hydrogenation. The relative stereochemistry of **14a** was confirmed using alternative reductive amination conditions. Hydrogenation over palladium on carbon was a much more suitable reaction for reducing **14a** in terms of reaction conditions, ease of workup, and diastereoselectivity. Under these conditions, the azide was reduced to the corresponding amine and an intramolecular condensation reaction ensued to form the cyclic imine **23a**, which was further reduced to the piperidine **24a** (Scheme 23).

Catalytic hydrogenation was carried out by stirring **14a** in EtOH with 10 mol% of palladium on carbon and under an atmosphere of hydrogen gas. The reaction was maintained at ambient temperature and a pressure of 500 p.s.i. using a high pressure Parr bomb. Upon completion, the reaction mixture was filtered through Celite providing a clear oil that could be further purified by flash chromatography to furnish piperidine **24a** which crystallized to a white solid upon sitting at the lab bench for a brief period of time. The relative stereochemistry of **24a** was determined by selective NOE and validated the stereochemistry that was assigned to major diastereomer **14a** (Scheme 23).

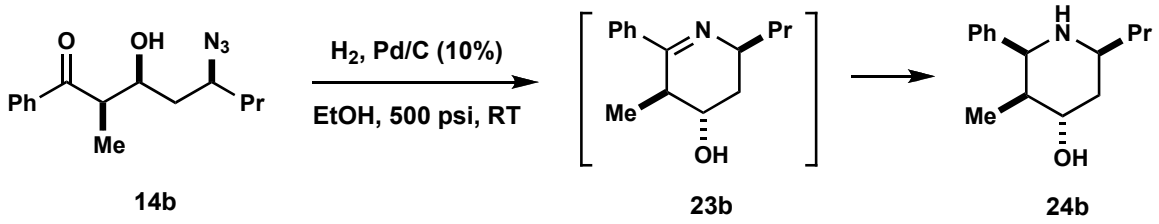
Scheme 23



The conformation of intermediate **23a** can be used to rationalize the diastereoselectivity seen with hydrogen reductions of six-membered imines, which are well known to be dictated by electrostatic effects like steric interactions and torsional strain developed during the reaction.[42] In this case, **23a** adopted a half-chair conformation that allowed the hydroxy and alkyl groups to assume equatorial positions. Hydrogen attack occurred via equatorial addition to the imine carbon (Scheme 23).

Stirring **14b** in EtOH with 10% palladium on carbon and under 500 p.s.i. of hydrogen gas afforded a mixture of **14b**, **24b**, and at least one other compound (Scheme 24). The nonselectivity of this reaction can be attributed to the 1,3-diaxial interactions that exist in the conformations of **23b** mentioned earlier (Scheme 21).

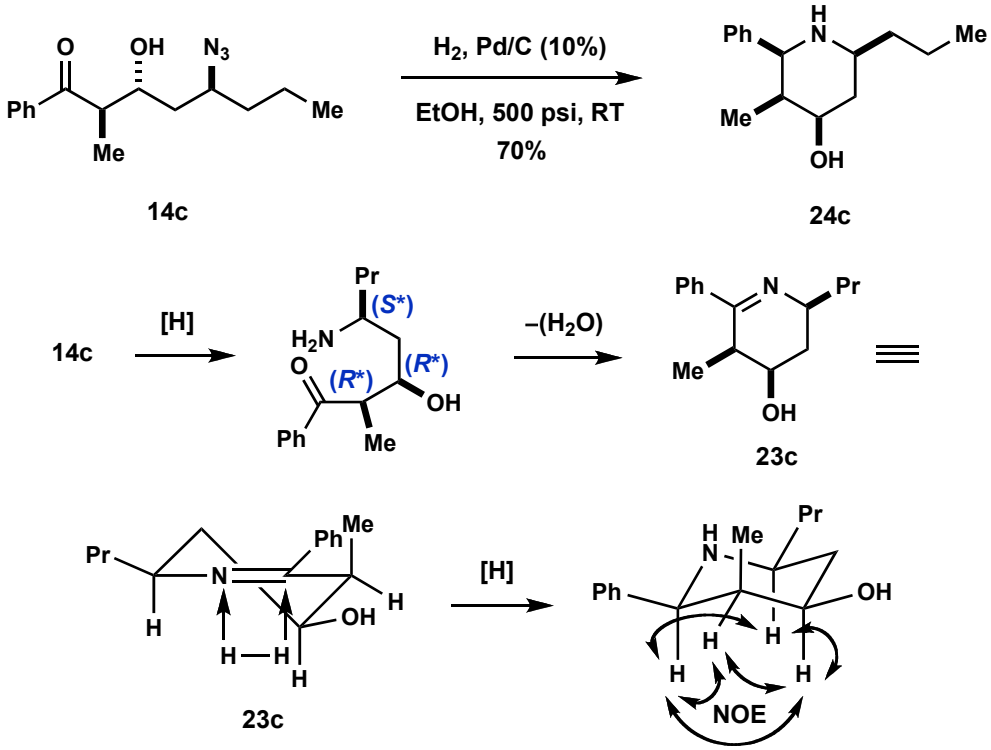
Scheme 24



14b **23b** **24b**

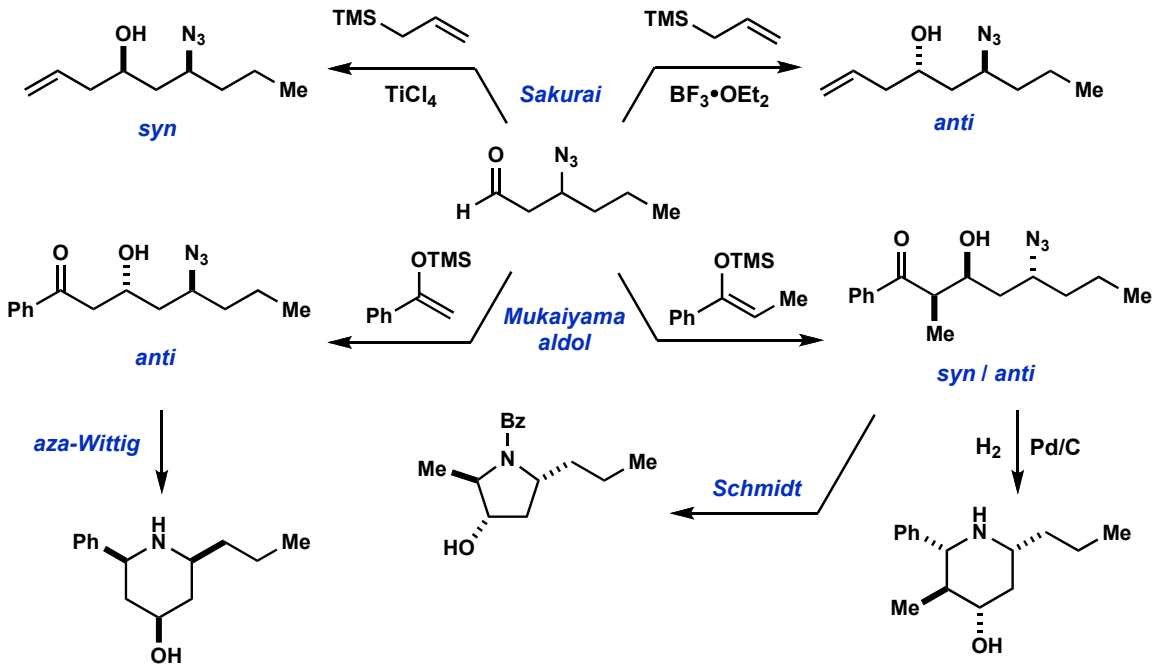
The relative stereochemistry of **14c** was determined from **24c** using catalytic hydrogenation. Isolated **14c** and 10 mol% of palladium on carbon were dissolved in EtOH and hydrogenated at 500 p.s.i. using a Parr bomb. The ^{1}H and ^{13}C NMR spectra of the crude reaction mixture showed that a single compound had been produced from the reaction. Further filtration through silica gel rendered a spectroscopically pure sample of product **24c**. The relative stereochemistry of **24c** and therefore, **14c**, was determined from NOE difference spectra, which indicated that the hydroxyl and all three of the alkyl substituents were adopting a *cis* relationship (Scheme 25). The stereofacial selectivity of the reductive amination could be explained with a half-chair conformation **23c** and hydrogenolysis of the imine from the π-face *trans* to the propyl and axial methyl group.[43]

Scheme 25



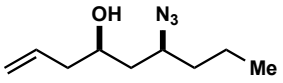
Summary. This study has revealed that Sakurai and Mukaiyama aldol nucleophilic additions to a *β*-azido aldehyde are generally diastereofacial selective (with the exception of $TiCl_4$-mediated allylations) in favor of forming the *anti* diastereomer, as well as being simple diastereoselective in favor of diastereomers showing *syn* relative stereochemistry. The addition products were cyclized with various intramolecular reactions that were diastereoselective when the stereocenters of the ensuing transition state intermediates were compatible with the reaction conditions. The substituted pyrrolidine and piperidine products were used for determining stereochemical assignments of the nucleophilic addition products and show how azido aldehydes serve as useful substrates for the short synthesis of biologically relevant *N*-heterocycles (Scheme 26).

Scheme 26

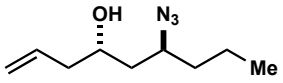

OH
N3
Me
syn
TMS
TiCl4
Sakurai
BF3•OEt2
anti
O
H
Ph
OTMS
Mukaiyama
aldol
syn / anti
aza-Wittig
Bz
N
HO
Schmidt
H2
Pd/C

EXPERIMENTAL SECTION

General procedures. All reagents used in this study were purchased from Sigma Aldrich. β-Azido hexanal **9** was generated from (*E*)-2-hexenal using slightly modified Boyer conditions.[32] Both silyl enol ethers **11** and **13** were prepared following previously reported procedures.[44] Unless otherwise noted, only dry solvents were used and all reactions were carried out in oven-dried flasks under an inert atmosphere of argon gas. ^{1}H and ^{13}C NMR spectra were generated from DRX 400 and 500 MHz Bruker instruments. Chemical shifts are given in parts per million downfield from internal tetramethylsilane. IR spectra were obtained with a Bio-Rad FTS-60A/896 FTIR spectrometer using KBr salt plates. HRMS (ESI^{+}) were obtained using a VG ZAB high resolution double focusing instrument. Analytical HPLC chromatograms were produced using a Shimadzu-VP liquid chromatography system.



(4*R**, 6*S**)-10a



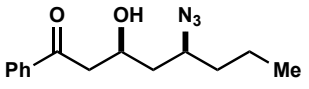
(4*S**, 6*S**)-10b

6-Azidonon-1-en-4-ol (10a, 10b). $TiCl_4$ procedure. Freshly prepared β-azido hexanal (±)-**9** (0.277 g, 1.96 mmol) and allyl trimethylsilane **5** (0.35 mL, 2.2 mmol) were dissolved in 24 mL of CH_2Cl_2. The mixture was cooled to -78 °C and $TiCl_4$ (0.24 mL, 2.2 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 45 min. The flask was removed from the cold bath and immediately quenched with the slow addition of saturated, aqueous NH_4Cl (24 mL). When stirring became impeded by the formation of ice, quenching was stalled until the mixture resumed adequate consistency.

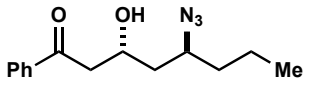
The biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated to give a crude oil. ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of **10a** : **10b** = 61 : 39. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as the mobile phase. The desired product was a clear, colorless oil and isolated in a 71% yield as a 61:39 ratio of diastereomers. Full characterization and relative stereochemistry of each diastereomer was previously determined by Shimizu and Nishi.[29] Major diastereomer (**10a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.32-1.59 (m, 5H), 1.61-1.67 (m, 1H), 2.13-2.32 (m, 2H), 2.45 (br s, 1H), 3.46 (p, 1H), 3.74-3.81 (m, 1H), 5.08-5.12 (m, 1H), 5.12-5.15 (m, 1H), 5.74-5.86 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.8, 19.1, 36.4, 40.7, 41.9, 60.4, 68.7, 118.3, 134.2. Minor diastereomer (**10b**, diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56-3.64 (m, 1H), 3.82-3.89 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.8, 19.3, 37.1, 41.3, 42.5, 59.5, 67.3, 118.3, 134.3.

6-Azidonon-1-en-4-ol (10a, 10b). BF_3•OEt_2 procedure. Freshly prepared *β*-azido hexanal (±)-**9** (0.214 g, 1.52 mmol) was dissolved in 24 mL of CH_2Cl_2. Allyl trimethylsilane **5** (0.26 mL, 1.6 mmol) was added to the solution. The mixture was cooled to -78 °C and BF_3•OEt_2 (0.21 mL, 1.7 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 3 h. The reaction was quenched with saturated, aqueous $NaHCO_3$ (24 mL), extracted, and concentrated as described above. ^{1}H NMR analysis on the crude reaction mixture indicated a diastereomeric ratio of **10a** : **10b** = 18 : 82. The crude product was purified by column chromatography on silica gel using 5% EtOAc in

hexanes as the mobile phase. The desired product was a clear, colorless oil and isolated in a 41% yield as a 16:84 ratio of diastereomers.



(3*R**, 5*R**)-12a

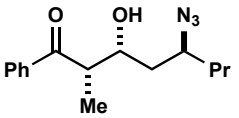


(3*R**, 5*S**)-12b

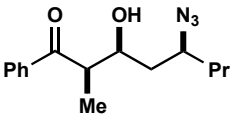
5-Azido-3-hydroxy-1-phenyloctan-1-one (3a, 3b). $TiCl_4$ procedure. Freshly prepared *β*-azido hexanal (±)-**9** (0.142 g, 1.01 mmol) and silyl enol ether **11** (0.211 g, 1.10 mmol) were dissolved in 24 mL of CH_2Cl_2. The mixture was cooled to -78 °C and 1.1 mL of a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 was added dropwise. The reaction mixture was stirred at -78 °C for 1 h. The flask was removed from the cold bath and immediately quenched with the slow addition of saturated, aqueous NH_4Cl (24 mL). When stirring became impeded by frozen ice, quenching was stalled until the mixture resumed adequate consistency. The biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated to give a crude oil. A sample of the crude oil was analyzed by HPLC (ratio of **12a** : **12b** = 23 : 77). The crude product was purified by column chromatography on silica gel (5% EtOAc in hexanes) to afford the product as a clear, colorless oil (52% yield, mixture of diastereomers). A pure sample of diastereomer **12b** was obtained by column chromatography (CH_2Cl_2). The relative stereochemistry of **12a** and **12b** was determined by conversion of **12b** to **22** as described below. TLC (*p*-anisaldehyde stain, CH_2Cl_2) **12b** R_f = 0.45, green spot, **12a** R_f = 0.36, purple spot. HPLC **12b** t_R = 4.3 min, **12a** t_R = 4.6 min (Alltech Econosil-CN column, 5 μm, 250 mm x 4.6 mm, 1% *i*-PrOH/hexane, flow rate 2.5 mL/min, oven 45 °C, UV 254 nm). Major

diastereomer (**12b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.39-1.67 (m, 5H), 1.70-1.81 (m, 1H), 3.09 (dd, *J* = 17.8 Hz, 1H), 3.20 (dd, *J* = 18.0, 2.8 Hz, 1H), 3.53 (dd, *J* = 3.6, 1.6 Hz, 1H), 3.70-3.79 (m, 1H), 4.47 (m, 1H), 7.46-7.51 (m, 2H), 7.62 (m, 1H), 7.94-7.99 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.9, 19.4, 37.3, 41.3, 45.2, 59.3, 64.7, 128.1, 128.8, 133.7, 136.6, 200.5. IR (CH_2Cl_2) 3400, 2100, 1680 cm^{-1}. HRMS calcd for $C_{14}H_{20}N_3O_2$: 262.1555. Found: 262.1564. Minor diastereomer (**12a**, diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-1.93 (m, 1H), 3.49 (m, *J* = 2.8 Hz, 1H), 3.61 (m, 1H), 4.39 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 19.2, 36.2, 40.5, 44.9, 59.7, 65.5, 200.3.

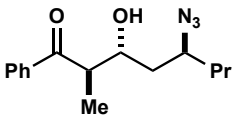
5-Azido-3-hydroxy-1-phenyloctan-1-one (12a, 12b). BF_3•OEt_2 procedure. Freshly prepared *β*-azido hexanal (±)-**9** (0.141 g, 1.00 mmol) was dissolved in 24 mL of CH_2Cl_2. The silyl enol ether **11** (0.215 g, 1.12 mmol) was added to the solution. The mixture was cooled to -78 °C and BF_3•OEt_2 (0.14 mL, 1.1 mmol) was added dropwise. The reaction was quenched after 1 h with saturated, aqueous $NaHCO_3$ (24 mL), extracted, and concentrated to give a crude oil as described above. A sample of the crude oil was analyzed by HPLC (ratio of **12a** : **12b** = 22 : 78). The product (clear, colorless oil) was obtained by column chromatography (5% EtOAc in hexanes) and isolated in a 66% yield as a mixture of diastereomers.



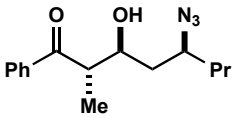
(2*S**, 3*R**, 5*S**)-14a



(2*R**, 3*S**, 5*S**)-14b



(2*R**, 3*R**, 5*S**)-14c



(2*S**, 3*S**, 5*S**)-14d

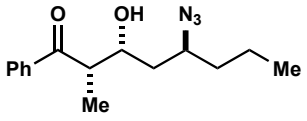
5-Azido-3-hydroxy-2-methyl-1-phenyloctan-1-one (14a, 14b, 14c, 14d). $TiCl_4$ procedure. Freshly prepared *β*-azido hexanal (±)-**9** (0.073 g, 0.52 mmol) and (*Z*)-silyl

enol ether **13** (0.204 g, 0.99 mmol) were dissolved in 24 mL of CH_2Cl_2. The mixture was cooled to -78 °C and 1.0 mL of a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 was added dropwise. The reaction mixture was stirred at -78 °C for 2 h. The flask was removed from the cold bath and immediately quenched with the slow addition of saturated, aqueous NH_4Cl (24 mL). When stirring became impeded by frozen ice, quenching was stalled until the mixture resumed adequate consistency. The biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated to give a crude oil. ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of **14a** : **14b** : **14c** : **14d** = 49 : 21 : 18 : 12. The relative stereochemistry of C-2, C-3, and C-5 for diastereomers **14a**, **14b**, and **14c** was determined through their conversions to **24a**, **24b**, and **24c**, respectively, as described below. Each of the three isomers **14a**, **14b**, and **14c** were separately cyclized under appropriate conditions to afford substituted piperidines suitable for NOE analysis and establishment of the relative stereochemistry present in the parent diastereomers (see below). The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as the mobile phase. The desired product was a clear, colorless oil and isolated in a 57% yield as a mixture of diastereomers (**14a** : **14b** : **14c** : **14d** = 50 : 17 : 19 : 14).

5-Azido-3-hydroxy-2-methyl-1-phenyloctan-1-one (14a, 14b, 14c, 14d). BF_3•OEt_2 procedure. Freshly prepared *β*-azido hexanal (±)-**9** (0.140 g, 0.99 mmol) and (*Z*)-silyl enol ether **13** (0.226 g, 1.10 mmol) were dissolved in 24 mL of CH_2Cl_2. The mixture was cooled to -78 °C and BF_3•OEt_2 (0.14 mL, 1.1 mmol) was added dropwise. The reaction was quenched after 1 h with saturated, aqueous $NaHCO_3$ (24 mL), extracted,

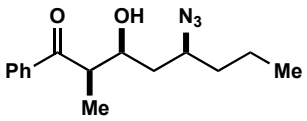
and concentrated to give a crude oil as described above. ^{1}H NMR analysis of the crude reaction mixture showed a diastereomeric ratio of **14a** : **14b** : **14c** : **14d** = 63 : 13 : 19 : 5. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as the mobile phase. The product was a clear, colorless oil and isolated in a 64% yield as a mixture of diastereomers (**14a** : **14b** : **14c** : **14d** = 59 : 14 : 21 : 5).

Diastereomers **14a**, **14b**, and **14c** could each be isolated as a single isomer by employing the following purification scheme on the complex mixture mentioned above. Separation of a mixture of **14a** and **14b** from a mixture of **14c** and **14d** could be achieved by column chromatography on silica gel using 5% EtOAc in hexanes. Separation of **14a** from **14b** could then be achieved *via* a second column of silica gel using 5-10% Et_2O in hexanes. Isolation of **14c** from the mixture with **14d** was achieved by stirring the mixture under Schmidt conditions ($TiCl_4$, CH_2Cl_2, 0 °C to room temperature). Unreacted **14c** was then readily isolated from reacted **14d** by purification through silica gel (5% EtOAc in hexanes).



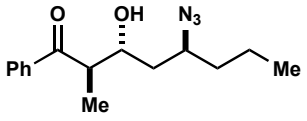
(2*S, 3*R**, 5*S**)-14a**

Major diastereomer **14a**: TLC (1 : 1, Hexanes/Et_2O) R_f = 0.48. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.2 Hz, 3H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.38-1.65 (m, 5H), 1.77 (ddd, *J* = 13.6, 10.4, 2.7 Hz, 1H), 3.41 (t, *J* = 2.0 Hz, 1H), 3.45 (qd, *J* = 7.2, 2.4 Hz, 1H), 3.69 (m, 1H), 4.31 (dq, *J* = 10.4, 2.5 Hz, 1H), 7.50 (m, 2H), 7.61 (m, 1H), 7.96 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.3, 13.9, 19.4, 37.4, 39.3, 44.9, 59.7, 68.1, 128.5, 128.8, 133.6, 135.6, 205.7. IR (CH_2Cl_2) 3500, 2100, 1680 cm^{-1}. HRMS calcd for $C_{15}H_{21}N_3NaO_2$: 298.1531. Found: 298.1550.



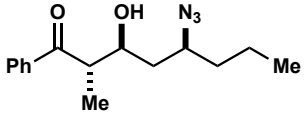
(2*R, 3*S**, 5*S**)-14b**

Diastereomer **14b**: TLC (1 : 1, Hexanes/Et_2O) R_f = 0.45. ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 7.2 Hz, 3H), 1.38-1.68 (m, 5H), 1.85 (ddd, *J* = 14.1, 9.0, 7.3 Hz, 1H), 3.31 (d, *J* = 2.0 Hz, 1H), 3.50 (qd, *J* = 7.2, 3.6 Hz, 1H), 3.57 (m, 1H), 4.20 (dq, *J* = 9.0, 2.7 Hz, 1H), 7.51 (m, *J* = 7.6 Hz, 2H), 7.62 (m, *J* = 7.4 Hz, 1H), 7.95-8.00 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.7, 13.9, 19.2, 36.1, 38.5, 44.8, 60.3, 69.2, 128.5, 128.8, 133.6, 135.8, 205.2. IR (CH_2Cl_2) 3500, 2100, 1670 cm^{-1}. HRMS calcd for $C_{15}H_{21}N_3NaO_2$: 298.1531. Found: 298.1558.



(2*R, 3*R**, 5*S**)-14c**

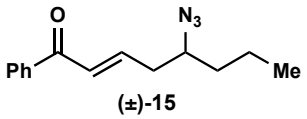
Diastereomer **14c**: TLC (4 : 1, Hexanes/EtOAc) R_f = 0.54. ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.40-1.69 (m, 6H), 3.21 (d, *J* = 6.7 Hz, 1H), 3.53 (qd, *J* = 7.2, 7.1 Hz, 1H), 3.74 (m, 1H), 4.11 (m, 1H), 7.51 (m, ca. 7.6 Hz, 2H), 7.62 (m, *J* = 7.4 Hz, 1H), 7.97 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.9, 15.7, 19.4, 37.3, 39.9, 46.1, 59.6, 70.9, 128.4, 128.8, 133.6, 136.3, 205.6. IR (CH_2Cl_2) 3500, 2100, 1680 cm^{-1}. HRMS calcd for $C_{15}H_{21}N_3NaO_2$: 298.1531. Found: 298.1556.



(2*S, 3*S**, 5*S**)-14d**

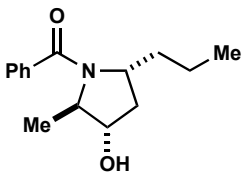
Diastereomer **14d**: TLC (4 : 1, Hexanes/EtOAc) R_f = 0.54. ^1H NMR (400 MHz, $CDCl_3$, diagnostic peaks only) δ 3.29 (d, *J* = 6.1 Hz, 1H), 4.02 (m, 1H); ^{13}C NMR (400

MHz, $CDCl_3$) δ 13.9, 15.2, 19.1, 36.0, 38.7, 45.8, 60.2, 71.6, 128.4, 128.8, 133.6, 136.3, 205.2.

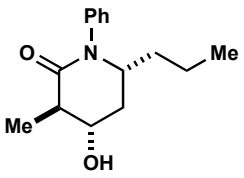


(±)-15

(*E*)-5-Azido-1-phenyloct-2-en-1-one (15). Major diastereomer **12b** (81 mg, 0.31 mmol) was dissolved in 12 mL of CH_2Cl_2 and added to a reaction vessel. While stirring at room temperature, BF_3•OEt_2 (0.1 mL, 0.8 mmol) was slowly added dropwise. The vessel was irradiated with MW at 60 °C for 5 min. TLC analysis indicated the presence of a new compound and incomplete consumption of the starting material. The reaction mixture was again irradiated with MW at 60 °C for 20 min. The starting material was still present by TLC. After MW at 80 °C for 10 min, TLC analysis indicated full consumption of starting material. The mixture was allowed to reach room temperature, and was quenched with 12 mL of saturated, aqueous $NaHCO_3$ solution. The biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude sample was purified by column chromatography on silica gel (5% EtOAc in hexanes). The product (±)-**15** (11 mg, 15% yield) was isolated as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (br t, ca. J = 7.1 Hz, 3H), 1.31-1.57 (m, 4H), 2.47 (m, 1H), 2.54 (s, 1H), 3.43 (m, 1H), 6.91-6.95 (m, 2H), 7.41 (m, 2H), 7.50 (m, 1H), 7.88 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.8, 19.3, 36.3, 37.7, 61.3, 128.3, 128.6, 128.6, 132.9, 137.6, 144.1, 190.3. IR (CH_2Cl_2) 2100, 1670, 1620 cm^{-1}. HRMS calcd for $C_{14}H_{17}N_3NaO$: 266.1269. Found: 266.1269.



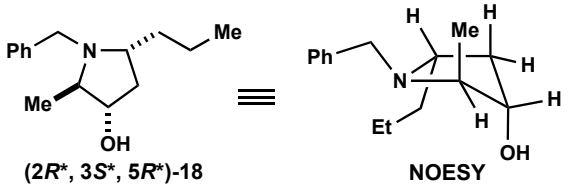
(2*R**, 3*S**, 5*R**)-16



(3*R**, 4*S**, 6*R**)-17
(possible structure)

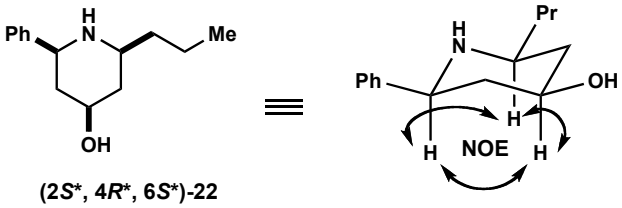
(2*R, 3*S**, 5*R**)-1-Benzoyl-3-hydroxy-2-methyl-5-propylpyrrolidine (16).** The azide **14a** (76 mg, 0.28 mmol) was dissolved in 20 mL of CH_2Cl_2 and cooled to 0 °C. $TiCl_4$ (1.0 M in CH_2Cl_2, 1.4 mL, 1.4 mmol) was slowly added dropwise. The mixture was allowed to reach room temperature. After stirring continuously for 3 days, the reaction mixture was again cooled to 0 °C and quenched with saturated, aqueous NH_4Cl (20 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated to give a dark red, crude oil. ^{1}H NMR analysis of the crude reaction mixture indicated an isomeric ratio of **16** : **17** = 61 : 39. The products were purified by flash column chromatography (5% to 100% EtOAc in hexanes) and isolated in 70% yield as a mixture of isomers (**16** : **17** = 62 : 38). The product mixture was a viscous, red oil that changed to light orange upon sitting. The relative stereochemistry of isomer **16** was determined by conversion to pyrrolidine **18** (see below). Although the identity of the minor component of the mixture was not determined, ^{1}H NMR data suggests that **17** is one possible structure. Major isomer (**16**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.71 (d, J = 6.6 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H), 1.08 (m, 1H), 1.37 (m, 1H), 1.70 (m, 1H), 1.83 (d, J = 13.9 Hz, 1H), 2.15 (m, 2H), 3.57 (br s, 1H), 3.95 (d, J = 3.3 Hz, 1H), 4.01 (m, 1H), 4.21 (t, J = 9.4 Hz, 1H), 7.31-7.55 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.1, 19.5, 19.8, 34.7, 36.1, 57.5, 64.1, 77.3, 127.2, 128.3, 129.7, 137.9, 171.2. IR (CH_2Cl_2) 3400, 1600

cm^{-1}. HRMS calcd for $C_{15}H_{22}NO_2$: 248.1651. Found: 248.1625. Minor mixture component (possibly **17**): ^1H NMR (500 MHz, $CDCl_3$) δ 0.50 (t, *J* = 6.4 Hz, 3H), 1.08 (m, 1H), 1.26 (d, *J* = 4.0 Hz, 3H), 1.37 (m, 2H), 1.70 (m, 1H), 1.88 (d, *J* = 13.8 Hz, 1H), 2.25 (m, 1H), 3.24 (br s, 1H), 4.01 (m, 1H), 4.07 (d, *J* = 2.9 Hz, 1H), 4.34 (q, *J* = 6.2 Hz, 1H), 7.31-7.55 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.2, 17.8, 19.3, 35.7, 37.4, 59.1, 63.0, 76.0, 126.7, 128.3, 129.6, 138.0, 170.6.



(2*R, 3*S**, 5*R**)-1-Benzyl-2-methyl-5-propylpyrrolidin-3-ol (18).** The mixture of amide isomers, **16** and **17** (**16** : **17** = 63 : 37, 71 mg, 0.29 mmol), were dissolved in 10 mL of THF and cooled to 0 °C. While stirring, a solution of $LiAlH_4$ (1.0M in Et_2O, 1.4 mL) was slowly added to the reaction flask. The reaction was allowed to slowly warm to room temperature and stirred for 42 h. After cooling to 0 °C, the reaction was slowly quenched with saturated, aqueous Rochelle's salt (sodium potassium tartrate, 20 mL). Approximately 15 mL of CH_2Cl_2 was then added and the mixture was transferred to a separatory funnel. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The extracts were combined, dried with Na_2SO_4, filtered, and concentrated to give a crude oil. ^1H NMR analysis of the crude reaction mixture indicated an isomeric ratio of 65 : 35. An analytical sample of **18** was obtained by flash chromatography using a stepwise gradient of increasing solvent polarity (400:0:0, 400:9.5:0.5, 350:9.5:0.5, 300:9.5:0.5 mL, CH_2Cl_2/MeOH/NH_4OH). The product **18** was

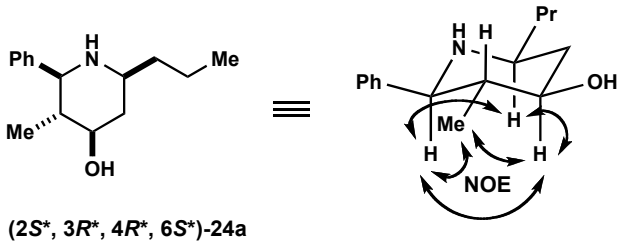
isolated alone as a pale, yellow oil (35 mg, 83% yield based on **16**). The relative stereochemistry of **18** was determined by 2D NOESY experiments. TLC (200 : 19 : 1, CH_2Cl_2/MeOH/NH_4OH) R_f = 0.40. ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.7 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H), 1.28-1.51 (m, 3H), 1.61 (dd, *J* = 14.2, 4.7 Hz, 1H), 1.71 (m, 1H), 2.38 (ddd, *J* = 14.7, 9.3, 5.9 Hz, 1H), 2.49 (br s, 1H), 2.80 (qq, *J* = 4.6, 4.3 Hz, 1H), 3.04 (q, *J* = 6.5 Hz, 1H), 3.54 (d, *J* = 13.7 Hz, 1H), 3.81 (d, *J* = 5.8 Hz, 1H), 3.96 (d, *J* = 13.7 Hz, 1H), 7.26 (m, *J* = 7.2 Hz, 1H), 7.34 (m, *J* = 7.5 Hz, 2H), 7.39 (m, *J* = 7.4 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 10.0, 14.5, 19.2, 36.9, 38.7, 51.2, 58.4, 62.8, 75.9, 126.8, 128.3, 128.4, 139.8. IR (CH_2Cl_2) 3400 cm^{-1}. HRMS calcd for $C_{15}H_{24}NO$: 234.1858. Found: 234.1844.



(2*S**, 4*R**, 6*S**)-22

(2*S, 4*R**, 6*S**)-2-Phenyl-6-propylpiperidin-4-ol (22).** Azide **12b** (0.136 g, 0.52 mmol) and PPh_3 (0.553 g, 2.11 mmol) were dissolved in 5 mL of THF and stirred at room temperature. After two days, the reaction mixture was cooled to 0 °C. $NaBH_4$ (0.049 g, 1.30 mmol), then MeOH (0.06 mL, 1.4 mmol) were added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with 10 mL of saturated, aqueous $NaHCO_3$ solution. The biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude sample was purified by column chromatography on silica gel (700:19:1, CH_2Cl_2/MeOH/NH_4OH). The product **22** (0.056

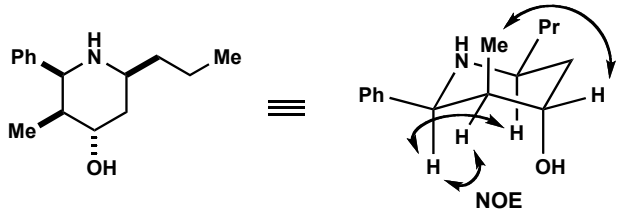
g, 49% yield) was isolated as a clear, colorless oil. The relative stereochemistry was confirmed by selective NOE experiments and matched previously reported data by Ma and Sun.[45] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.17 (q, *J* = 11.3 Hz, 1H), 1.34-1.44 (m, 2H), 1.44-1.53 (m, 3H), 1.85-2.17 (m, 4H), 2.73 (m, 1H), 3.67 (dd, *J* = 11.5, 2.3 Hz), 3.79 (m, 1H), 7.28 (m, 1H), 7.35 (m, 2H), 7.39 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.2, 19.2, 38.9, 41.6, 43.7, 55.1, 59.8, 69.7, 126.8, 127.3, 128.5, 144.1.



(2*S, 3*R**, 4*R**, 6*S**)-24a**

(2*S, 3*R**, 4*R**, 6*S**)-3-Methyl-2-phenyl-6-propylpiperidin-4-ol (24a).** Major diastereomer, **14a** (18 mg, 0.065 mmol), was dissolved in 2 mL of EtOH and transferred to a small glass vial. A stir bar and Pd/C (10% by weight, 26 mg, 0.03 mmol) were added and the uncapped vial was placed into a high-pressure Parr bomb. The mixture was stirred at room temperature and hydrogenated at a pressure of 500 p.s.i. for 1 d. The crude product was filtered through Celite and rinsed with 10% MeOH in CH_2Cl_2 (ca. 80 mL). The filtrate was concentrated *in vacuo* to give a clear, colorless oil. The product was purified by flash chromatography using a stepwise gradient of increasing solvent polarity (0, 0.5, 1, 2, 3, 4, 5, 6 mL : 200 mL, 5% NH_4OH in MeOH : CH_2Cl_2) and isolated as a clear, colorless oil (13 mg, 87% yield) that changed to a white solid over time. The relative stereochemistry was confirmed by selective NOE experiments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (d, *J* = 6.5 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H), 1.24 (m, 3H), 1.33 (m, 2H), 1.50 (dq, *J* = 16.3, 3.3 Hz, 1H), 1.86 (br s, 2H), 1.97 (dq, *J* = 12.1, 2.3

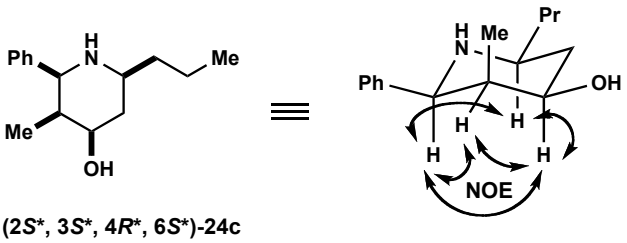
Hz, 1H), 2.66 (dtd, J = 11.1, 6.3, 2.3 Hz, 1H), 3.16 (d, J = 10.0 Hz, 1H), 3.27 (td, J = 10.1, 4.6 Hz, 1H), 7.18 (m, 1H), 7.25 (m, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.2, 14.2, 19.1, 38.9, 41.8, 45.3, 55.2, 67.2, 75.1, 127.5, 128.1, 128.4, 142.7. IR (CH_2Cl_2) 3300 cm^{-1}. HRMS calcd for $C_{15}H_{24}NO$: 234.1858. Found: 234.1847.



(2*S**, 3*S**, 4*S**, 6*S**)-24b

(2*S, 3*S**, 4*S**, 6*S**)-3-Methyl-2-phenyl-6-propylpiperidin-4-ol (24b).** Diastereomer **14b** (46 mg, 0.17 mmol) and PPh_3 (191mg, 0.73 mmol) were dissolved in THF (15 mL) and stirred at room temperature for 4 d. The reaction mixture was cooled to -78 °C and a solution of $LiBH_4$ (35 mg, 1.61 mmol) in THF (6 mL) was slowly added. The mixture was stirred to room temperature. At 0 °C, the reaction was quenched with saturated, aqueous $NaHCO_3$ (25 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The ether solution was dried with Na_2SO_4, filtered, and concentrated. The crude compound was purified by flash chromatography using a stepwise gradient of increasing solvent polarity (0, 0.25, 0.5, 1, 2, 3, 4, 5 mL : 200 mL, 5% NH_4OH in MeOH : CH_2Cl_2). The product was isolated as a clear, colorless oil (23 mg, 58% yield). The relative stereochemistry was confirmed by selective NOE experiments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73 (d, J = 7.2 Hz, 3H), 0.94 (t, J = 7.1 Hz, 3H), 1.32-1.52 (m, 4H), 1.56-1.66 (m, 2H), 1.75-2.05 (m, 3H), 3.11 (m, 1H), 3.98 (q, J = 2.6 Hz, 1H), 4.37 (d, J = 3.1 Hz, 1H), 7.23 (m, J = 6.9, 1.6 Hz, 1H), 7.30-7.37 (m, 4H);

^{13}C NMR (500 MHz, $CDCl_3$) δ 11.2, 14.3, 19.0, 34.6, 39.2, 41.8, 51.5, 58.0, 71.8, 126.5, 126.7, 128.1, 143.7. IR (CH_2Cl_2) 3400 cm^{-1}. HRMS calcd for $C_{15}H_{24}NO$: 234.1858. Found: 234.1846.



(2*S, 3*S**, 4*R**, 6*S**)-24c**

(2*S, 3*S**, 4*R**, 6*S**)-3-Methyl-2-phenyl-6-propylpiperidin-4-ol (24c).** Diastereomer **14c** (96 mg, 0.35 mmol) was dissolved in 4 mL of EtOH and transferred to a small glass vial. A stir bar and Pd/C (10% by weight, 37 mg, 0.03 mmol) were added and the uncapped vial was placed into a high-pressure Parr bomb. The mixture was stirred at room temperature and hydrogenated at a pressure of 500 p.s.i. for 4 h. The crude product was filtered through Celite, rinsed with 10% MeOH in CH_2Cl_2 (ca. 80 mL), and concentrated to an oil. The product was purified by flash chromatography using a stepwise gradient of increasing solvent polarity (0, 1, 2, 3, 4, 5 mL : 200 mL, 5% NH_4OH in MeOH : CH_2Cl_2) and isolated as a white solid (57 mg, 70% yield). The relative stereochemistry was confirmed by selective NOE difference experiments. TLC (200 : 19 : 1, CH_2Cl_2/MeOH/NH_4OH) R_f = 0.36. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.71 (d, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H), 1.31-1.58 (m, 5H), 1.74 (dt, *J* = 12.2, 3.2 Hz, 1H), 1.97 (br s, 2H), 2.13 (m, 1H), 2.73 (dtd, *J* = 11.1, 6.2, 2.7 Hz, 1H), 3.89 (d, *J* = 2.8 Hz, 1H), 3.98 (dt, *J* = 11.7, 4.7 Hz, 1H), 7.26 (m, 1H), 7.34 (m, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 5.2, 14.3, 19.2, 35.3, 38.9, 41.3, 55.2, 62.7, 72.7, 126.6, 126.7, 128.1, 143.1. IR (CH_2Cl_2) 3400 cm^{-1}. HRMS calcd for $C_{15}H_{24}NO$: 234.1858. Found: 234.1848.

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